NOVARTIS

Global Clinical Development - General Medicine

AIN457/Secukinumab

Clinical Trial Protocol CAIN457H2315 / NCT02696031

A randomized, double-blind, placebo-controlled multicenter study of secukinumab 150 mg in patients with active non-radiographic axial spondyloarthritis to evaluate the safety, tolerability and efficacy up to 2 years, followed by an optional phase of either 150 mg or 300 mg randomized dose escalation for up to another 2 years

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List of abbreviations

AE	adverse event
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ANCOVA	analysis of covariance
AS	Ankylosing Spondylitis
ASAS	Ankylosing SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
axSpA	Axial Spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BSL	baseline
BOCF	Baseline observation carried forward
CFR	Code of Federal Regulation
COX	Cyclooxygenase
CPO	country pharma organization
(e)CRF	electronic case report form
CRO	contract research organization
CRP (hsCRP)	(high sensitivity) C-reactive protein
CRP+	Patient with a CRP value above the ULN at screening
DMARD	disease modifying anti-rheumatic drug
DNA	deoxyribonucleic acid
DS&E	Drug Safety and Epidemiology
ECG	electrocardiogram
EDC	electronic data capture
EDTA	ethylenediamine-tetraacetic acid
EEA	European Economic Area
ELISA	enzyme-linked immuno sorbent assay
EMA/EMEA	European Medical Agency
[redacted]	[redacted]

EU	European Union
eSource	electronic Source Data Capturing Tool
[redacted]	[redacted]
[redacted]	[redacted]
FDA	Food and Drug Administration
FAS	full analysis set
GCP	good clinical practice
GDPR	General Data Protection Regulation
GGT	gamma-glutamyl-transferase
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC/EC	Independent Ethics Committee
IFU	Instructions for Use
IQS	Integrated Quantitive Sciences
IL	interleukin
IN	Investigator Notification
IRB	Institutional Review Board
IRT	interactive response technology
i.v.	intravenous(ly)
LLN	lower limit of normal
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MAR	missing at random
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model repeated measures
MRI	magnetic resonance imaging

MRI+	Patient with a MRI considered positive for sacroiliitis at screening
[redacted]	[redacted]
MTX	methotrexate
nr-axSpA	non-radiographic axial spondyloarthritis
NSAID	non-steroidal anti-inflammatory drug
PCS	Physical Component Summary
[redacted]	[redacted]
PFS	pre-filled syringe
[redacted]	[redacted]
[redacted]	[redacted]
PoC	proof of concept
PPD	purified protein derivative
PRN	pro re nata
PRO	patient reported outcome
PsA	psoriatic arthritis
OC/RDC	Oracle clinical/remote data capture
QoL	quality of life
RA	rheumatoid arthritis
RoW	Rest of World
SAE	serious adverse event
SCR	screening
s.c.	subcutaneous(ly)
SD	Standard Deviation
SF-36	Short Form-36
SIJ/SI Joint	Sacroiliac Joint
SpA	Spondyloarthritis
STIR	Short tau inversion recovery
SUSAR	suspected unexpected serious adverse reaction
t.i.d.	ter in die, three times a day
TB	Tuberculosis
TNF/TNFα	Tumor Necrosis Factor
TNF-IR	TNFα inhibitor inadequate responder

ULN	upper limit of normal
USA	United States of America
VAS	visual analog scale
WBC	White Blood Cell
[redacted]	[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical Epochs are: screening / wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
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* protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Period	A subdivision of a cross-over study
Premature subject/patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Amendment 1

Amendment rationale

This protocol amendment is issued for the following reasons:

Based on a meta-analysis from unpublished studies with secukinumab, the powering of the study was re-evaluated. This new evaluation triggered a changed order in the testing hierarchy as well as adjustments of the population for the primary endpoint to TNF naïve patients only. These changes ensure that the placebo population will remain the same size and the randomization will continue to be 2:1 for the active to placebo ratio, while maintaining adequate power for primary and secondary analyses.

After the study was initiated, feedback from the FDA requested a focus on the no-load dosing regimen, which is reflected in the changes to Analysis Plan B. In alignment with that, Analysis Plan A evaluates the dosing regimen approved in countries outside of the US, which is reflected in its focus on the load regimen.

The test for HLA-B27 is moved from the baseline visit to screening visit 2 to facilitate the screening process for the sites.

The maximally allowed proportion of TNF-IR patients was changed from 30% to 20%, based on the aforementioned meta-analysis from unpublished studies with secukinumab and due to the changes in the statistical hierarchy, as well as the unavailability of response rates for biologics in TNF-IR patients to validate power calculation assumptions. Additionally, due to the long wash out required for some TNF-IR patients, enrolment of TNF-IR patients will end two months prior to the projected end of the screening period.

Historic MRI will be accepted, if taken within 3 months of baseline and in alignment of the imaging criteria to facilitate the re-screening process for patients and sites.

The wording in the SAE reporting section was updated to be aligned with current and future SAE reporting processes.

A decision was taken to replace the eSource system and collect the data for the study in OC/RDC in all countries. This process change will be reflected in the respective sections where eSource is mentioned.

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

Changes to the protocol

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

The wording of various sub-sections to “Study objectives” (Section 2), “Investigational Plan” (Section 3), “Population” (Section 4), “Treatment” (Section 5), “Visit schedule and assessments” (Section 6), “Safety Monitoring” (Section 7), “Data review and database management” (Section 8), and “Data analysis” (Section 9) have been amended to reflect the rationale given above.

Additionally, this protocol amendment includes the correction of typographical and formatting errors and minor editorial changes for increased clarity of the text. Consequently, a small number of changes were implemented throughout the protocol.

None of the changes described in this amended protocol are made due to newly emerged safety considerations.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Amendment 2

Amendment rationale

This protocol amendment is issued to add an extension phase to the current core protocol. This extension phase will consist of two treatment periods, a 16-week blinded dose escalation treatment period followed by a blinded treatment period lasting until the last patient has reached the end of the 16-week dose escalation treatment period. Before a patient will be able to participate in this additional 16-week treatment escalation period, a new informed consent form (ICF) has to be signed.

The order of the secondary endpoints of the analysis plan B in the hierarchy was updated to elevate several Load regimen endpoints to reflect their clinical relevance.

The wording for the Withdrawal of Consent section was updated to align with the European Economic Area (EEA) General Data Protection Regulation (GDPR) requirements.

Changes to the protocol

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

The wording of various sub-sections to “Introduction” (Section 1), “Study objectives” (Section 2), “Investigational Plan” (Section 3), “Population” (Section 4), “Treatment” (Section 5), “Visit schedule and assessments” (Section 6), “Data analysis” (Section 9), “References” (Section 12), and “Appendices” (Section 13) have been amended to reflect the rationale given above.

Additionally, this protocol amendment includes the correction of typographical and formatting errors and minor editorial changes for increased clarity of the text. Consequently, a small number of changes were implemented throughout the protocol.

None of the changes described in this amended protocol are made due to newly emerged safety considerations.

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The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Protocol summary

Protocol number	CAIN457H2315
Title	A randomized, double-blind, placebo-controlled multicenter study of secukinumab 150 mg in patients with active non-radiographic axial spondyloarthritis to evaluate the safety, tolerability and efficacy up to 2 years, followed by an optional phase of either 150 mg or 300 mg randomized dose escalation for up to another 2 years
Brief title	Study of efficacy and safety of secukinumab in patients with non-radiographic axial spondyloarthritis
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug; Biologic
Study type	Interventional
Purpose and rationale	To demonstrate the clinical efficacy, safety and tolerability of secukinumab compared to placebo in patients with nr-axSpA at Week 16 as well as Week 52 and long term efficacy and safety up to Week 104 followed by an optional 16-week randomized dose escalation treatment period and a continuous treatment period for up to Week 208.
Primary Objective(s)	**ANALYSIS PLAN A - EU and other non- USA Regions** To demonstrate superiority of secukinumab 150 mg s.c. with loading over placebo at Week 16, based on the proportion of TNF naïve patients achieving an ASAS40 response (Assessment of SpondyloArthritis International Society criteria). **ANALYSIS PLAN B - USA** To demonstrate superiority of secukinumab 150 mg s.c. without loading over placebo at Week 52, based on the proportion of TNF naïve patients achieving an ASAS40 response (Assessment of SpondyloArthritis International Society criteria)
Secondary Objectives	**ANALYSIS PLAN A** 1. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the proportion of all patients achieving an ASAS40 response 2. To demonstrate that the efficacy of secukinumab 150 mg s.c., without loading, at Week 16 is superior to placebo based on the proportion of TNF naive patients achieving an ASAS40 response 3. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 16 is superior to placebo based on the proportion of patients meeting the ASAS 5/6 response criteria 4. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 16 is superior to placebo based on the change from baseline in total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 5. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 16 is superior to placebo based on the proportion of patients achieving BASDAI 50

	6. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the change from baseline of high sensitivity C-Reactive Protein (hsCRP) 7. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 16 is superior to placebo based on the change from baseline in total Bath Ankylosing Spondylitis Functional Index (BASFI) 8. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 16 is superior to placebo based on the change from screening in sacroiliac (SI) joint edema on MRI 9. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the proportion of subjects achieving an ASAS20 response 10. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 16 is superior to placebo based on the change from baseline in Short Form-36 Physical Component Summary (SF-36 PCS) 11. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) scores 12. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 16 is superior to placebo based on the proportion of patients achieving ASAS partial remission 13. Overall safety and tolerability of secukinumab **ANALYSIS PLAN B** 1. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 52 is superior to placebo based on the proportion of all patients achieving an ASAS40 response 2. To demonstrate that the efficacy of secukinumab 150 mg s.c., with loading, at Week 52 is superior to placebo based on the proportion of TNF naive patients achieving an ASAS40 response 3. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the proportion of subjects achieving an ASAS40 response 4. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 16 is superior to placebo based on the change from baseline in total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 5. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 16 is superior to placebo based on the proportion of patients achieving BASDAI 50 6. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 52 is superior to placebo based on the proportion of patients achieving BASDAI 50 7. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the change from baseline of high sensitivity C-Reactive Protein (hsCRP) 8. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 16 is superior to placebo based on the

	change from baseline in Short Form-36 Physical Component Summary (SF-36 PCS) To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) scores 9. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 16 is superior to placebo based on the proportion of patients meeting the ASAS 5/6 response criteria 10. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the proportion of subjects achieving an ASAS20 response 11. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 16 is superior to placebo based on the change from baseline in total Bath Ankylosing Spondylitis Functional Index (BASFI) 12. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 16 is superior to placebo based on the change from screening in SI joint edema on MRI 13. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 52 is superior to placebo based on the proportion of patients achieving Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-Reactive Protein (CRP) inactive disease as defined by ASDAS < 1.3 14. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 52 is superior to placebo based on the change from screening in SI joint edema on MRI 15. To demonstrate that the efficacy of secukinumab 150 mg s.c. with or without loading at Week 52 is superior to placebo based on the change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) scores 16. Overall safety and tolerability of secukinumab
Study design	This is a randomized, double-blind, placebo-controlled study
Population	The study population will consist of 555 male and female patients (≥ 18 years old at the time of consent) fulfilling the ASAS classification criteria for axSpA, with no radiographic evidence of changes in the sacroiliac joints that would meet the modified New York criteria for AS.

Inclusion criteria	• Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study assessment is performed
	• Male or non-pregnant, non-nursing female patients at least 18 years of age
	• Diagnosis of axSpA according to ASAS axSpA criteria:
	  • Inflammatory back pain for at least 6 months
	  • Onset before 45 years of age
	  • Sacroiliitis on MRI with ≥ 1 SpA feature OR HLA-B-27 positive with ≥2 SpA features
	• Objective signs of inflammation **at screening**, evident by
	  Either MRI with Sacroiliac Joint inflammation
	  OR hsCRP > ULN (as defined by the central lab)

	• Active axSpA as assessed by total BASDAI ≥ 4 cm (0-10 cm) **at baseline**
	• Spinal pain as measured by BASDAI question #2 ≥ 4 cm (0-10 cm) **at baseline**
	• Total back pain as measured by VAS ≥ 40 mm (0-100 mm) **at baseline**
	• Patients should have been on at least 2 different NSAIDs at the highest recommended dose for at least 4 weeks in total prior to randomization with an inadequate response or failure to respond, or less if therapy had to be withdrawn due to intolerance, toxicity or contraindications
	• Patients who are regularly taking NSAIDs (including COX-2 inhibitors) as part of their axSpA therapy are required to be on a stable dose for at least 2 weeks before randomization
	• Patients who have been on a TNFα inhibitor (not more than one) must have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months prior to randomization or have been intolerant to at least one administration of an anti-TNFα agent
	• Patients who have previously been on a TNFα inhibitor will be allowed entry into study after an appropriate wash-out period prior to randomization:
	  • 4 weeks for Enbrel® (etanercept) – with a terminal half-life of 102 ± 30 hours (s.c. route)
	  • 8 weeks for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (i.v. infusion)
	  • 10 weeks for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route)
	  • 10 weeks for Simponi® (golimumab) – with a terminal half-life of 11-14 days
	  • 10 weeks for Cimzia® (certolizumab) – with a terminal half-life of 14 days
	• Patients taking 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
	• Patients on MTX must be on stable folic acid supplementation before randomization
	• Patients who are on a DMARD other than MTX or sulfasalazine must discontinue the DMARD 4 weeks prior to randomization, except for leflunomide, which has to be discontinued for 8 weeks prior to randomization unless a cholestyramine washout has been performed
	• Patients taking systemic corticosteroids have to be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization
	For extension phase:
	• Written informed consent must be obtained before any assessment is performed.
	• Patients who have completed the full study treatment period (104 weeks) in the core phase on study treatment.

Exclusion criteria	• Patients with radiographic evidence for sacroiliitis, grade ≥ 2 bilaterally or grade ≥ 3 unilaterally (radiological criterion according to the modified New York diagnostic criteria for AS) as assessed by central reader • Inability or unwillingness to undergo MRI (e.g., patients with pacemakers, aneurysm clips or metal fragments / foreign objects in the eyes, skin or body) • 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 • Patients taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine) • Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor • Use of any investigational drug and/or devices within 4 weeks of randomization, or a period of 5 half-lives of the investigational drug, whichever is longer • History of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes • Any therapy by intra-articular injections (e.g., corticosteroid) within 4 weeks before randomization • Any intramuscular corticosteroid injection within 2 weeks before randomization • Patients previously treated with any biological immunomodulating agents, except those targeting TNFα • Patients who have taken more than one anti-TNFα agent • 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) • Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during entire study or longer if required by locally approved prescribing information. • Active ongoing inflammatory diseases other than axSpA that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease or uveitis • Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions, which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy • Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥ 160/95 mmHg), congestive heart failure (New York Heart Association

	status of class III or IV), uncontrolled diabetes, or very poor functional status unable to perform self-care • History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin. • 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) • 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) • Active systemic infections during the last two weeks prior to randomization (exception: common cold) • 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. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment according to local country guidelines must have been initiated • Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening or randomization • History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed) • Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial • Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins) • Inability or unwillingness to receive injections with PFS • 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 • Donation or loss of 400 mL or more of blood within 8 weeks before dosing • History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization • Plans for administration of live vaccines during the study period or 6 weeks prior to randomization
Investigational and reference therapy	Secukinumab 150 mg s.c. Matching placebo

Efficacy assessments	• Assessment of SpondyloArthritis International Society criteria (ASAS) • Patient's global assessment of disease activity (VAS) • Patient's assessment of back pain intensity (VAS) • Bath Ankylosing Spondylitis Functional Index (BASFI) • Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) • [redacted] • [redacted] • hsCRP [redacted] • [redacted], ASDAS-CRP [redacted] response categories • [redacted] • MRI of spine and sacroiliac joints • [redacted] • X-ray of the sacroiliac joints
Safety assessments	• QuantiFERON TB-Gold test or PPD skin test • Chest X-ray or MRI • Physical examination • Vital signs • Height and weight • Laboratory evaluations • [redacted] • Electrocardiogram • Pregnancy and assessment of fertility • Local tolerability (Injection site reactions) • Tolerability of secukinumab
Other assessments	• Health-related Quality of Life SF-36 ASQoL [redacted] • HLA-B27 [redacted]
Data analysis	The statistical hypothesis for ASAS40 being tested is that there is no difference in the proportion of patients fulfilling the ASAS40 criteria at Week 16 (analysis plan A) or 52 (analysis plan B), respectively in the secukinumab regimens versus placebo regimen
Key words	Non-radiographic spondyloarthritis, chronic inflammatory disease, inflammatory back pain, secukinumab, AIN457

1 Introduction

1.1 Background

Axial Spondyloarthritis (axSpA) is a group of rheumatic disorders with spinal inflammation and inflammatory back pain as common denominator. 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 according to the Assessment of Spondyloarthritis international Society (ASAS) classification criteria (Rudwaleit et al 2009) for axSpA if they fulfill either the clinical arm or the imaging arm of the criteria.

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

The 2009 ASAS classification criteria for axSpA were introduced to establish standards that apply to patients with or without radiographic sacroiliitis by including both X-ray and MRI as imaging modalities. The diagnosis of nr-axSpA based on imaging can achieve up to 88% specificity and 67% sensitivity whilst diagnosis based on clinical parameters only achieve approximately 83% specificity and 57% sensitivity when based on clinical parameters only (Sieper and van der Heijde 2013). In addition to the differential identification of AS and nr-axSpA patients, the ASAS criteria allow for the implementation of clinical trials in the treatment of nr-axSpA, a disease entity for which there is an unmet medical need (Sieper 2012).

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 do AS patients (Wallis et al 2013). Commonality of etiopathogenic characteristics and natural history of AS and nr-axSpA is the subject of ongoing research. 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). Progression from nr-axSpA to AS was observed in about 12% of nr-axSpA patients over the course of 2 years (Poddubnyy et al 2011). However, it is estimated that 10-15% of nr-axSpA patients do not develop radiographic sacroiliitis (Sieper and van der Heijde 2013).

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered first-line therapy for all patients with axSpA. Traditional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and sulfasalazine are not effective in the treatment of axSpA. Anti-TNF agents are approved therapies for patients with AS who continue to have active disease despite NSAIDs. In Europe, several anti-TNF agents are also approved for nr-axSpA. However, more than 60% of nr-axSpA patients treated with adalimumab or etanercept did not achieve an ASAS40 response in randomized clinical trials (Sieper et al 2013, Dougados et al 2014). Moreover, TNF blockade does not result in long term remission in AS and responders usually relapse within a few weeks after interruption of treatment (Baraliakos et al 2005). Whilst effective in treating the inflammatory symptoms, TNF antagonists do not prevent structural

damage of the joints in AS (van der Heijde et al 2008a, van der Heijde et al 2008b). Currently, there is no experimental evidence that early therapy with approved treatment options in patients with nr-axSpA can prevent or delay the occurrence of structural alterations of the axial skeleton, which usually develop over a period of up to 10 years (Robinson et al 2013).

Secukinumab (AIN457) is a high-affinity recombinant, fully human monoclonal anti-human Interleukin-17A antibody of the IgG1/κ-class. Secukinumab binds to human IL-17A and neutralizes the bioactivity of this cytokine. IL-17A is the central lymphokine of a newly defined subset of inflammatory T cells (Th17) which appear to be pivotal in several autoimmune and inflammatory processes in some animal models. IL-17A is mainly produced by memory CD4+ and CD8+ T lymphocytes and is being recognized as one of the principal pro-inflammatory cytokines in immune mediated inflammatory diseases. Assuming a potential role of Th17 cells in the inflammatory infiltrate in spondyloarthritides, it can be speculated that the activity of inflammation in early disease stages, such as nr-axSpA and the ensuing structural changes in axial joints over the longer term, characteristic of axSpA may be amenable to modulation via IL-17 antagonism.

AS (one of the Radiographic axial SpAs) Phase III studies showed an ASAS40 response rate of 36.1% at Week 16 to secukinumab (150 mg s.c. at Weeks 0, 1, 2, and 3, followed by the same dose every 4 weeks). A statistically significant difference in ASAS40 response between the secukinumab 150 mg group and placebo was evident as early as at Week 2. In the Phase II study in AS, MRI imaging performed at baseline and at Weeks 6 and 28 showed a reduction of inflammation after 6 weeks which was maintained up to Week 28. Early improvements were especially noted in patients with higher baseline MRI scores (Baraliakos et al 2011).

As of 12-Jul-2015, approximately 12000 healthy subjects and patients have been enrolled into clinical trials with secukinumab, of which approximately 9600 have received at least one dose of secukinumab. Overall, secukinumab trials have included various indications (Rheumatoid Arthritis (RA), AS, Psoriatic Arthritis (PsA), psoriasis, multiple sclerosis, uveitis, Crohn's disease, dry eye syndrome, polymyalgia rheumatica) at doses ranging from single and multiple doses of 0.1 mg/kg to 30 mg/kg i.v. and 25 mg to 300 mg subcutaneous(ly) (s.c.). As of March 2015, Secukinumab is now approved for the treatment of psoriasis in the European Union (EU), the US, and Japan. Full safety results from completed studies for PsA, AS and psoriasis show that secukinumab generally is safe and well tolerated. Please refer to the Investigator's Brochure (IB) for a more detailed review of the risk : benefit profile of secukinumab which supports the clinical development for the treatment of nr-axSpA patients with secukinumab.

As most studies for currently marketed biologic treatments for axSpA (with and without radiologic evidence) have failed to show evidence of slowing-down or even stopping the structural progression of the disease, there is an unmet medical need for new therapies being able to stop this structural damage.

1.2 Purpose

The purpose of this study is to demonstrate the clinical efficacy, safety and tolerability of two different regimens of secukinumab, with loading and without loading, compared to placebo in patients with nr-axSpA at Week 16 as well as Week 52. Additionally, 1 year progression of structural changes as evidenced by MRI will be assessed at Week 52. This study will also observe the long-term efficacy, safety, and tolerability of secukinumab and the evolution of

radiographic correlates of inflammation and structural progression based on the MRI and X-ray results up to Week 104.

At the end of the core phase, an optional 16-week randomized dose escalation treatment period will assess if a treatment escalation from 150 mg to 300 mg secukinumab is of further benefit to patients, as compared to continuous treatment with 150 mg secukinumab. Additionally, long-term efficacy, safety and tolerability of the 300 mg dose will be assessed in a treatment follow-up phase.

2 Study objectives

2.1 Primary objective(s)

There are two primary objectives based on regional regulatory precedent and feedback. These objectives will be tested in separate analysis plans.

ANALYSIS PLAN A - EU and other non-United States of America (USA) Regions

To demonstrate superiority of secukinumab 150 mg s.c. with loading over placebo at Week 16, based on the proportion of TNF naïve patients achieving an ASAS40 response (Assessment of SpondyloArthritis International Society criteria).

ANALYSIS PLAN B - USA

To demonstrate superiority of secukinumab 150 mg s.c. without loading over placebo at Week 52, based on the proportion of TNF naïve patients achieving an ASAS40 response (Assessment of SpondyloArthritis International Society criteria)

2.2 Secondary objectives

ANALYSIS PLAN A

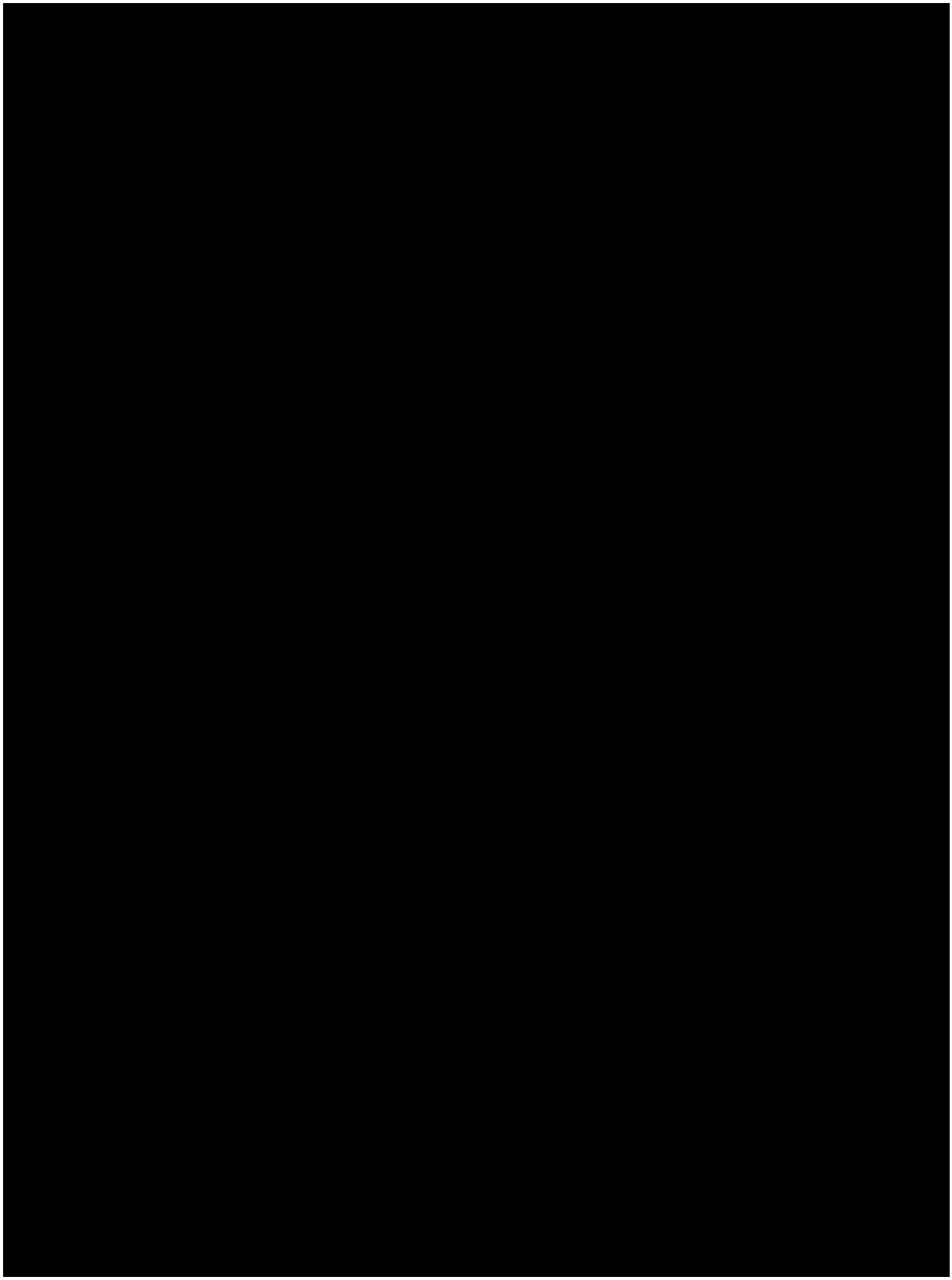
1. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the proportion of all patients achieving an ASAS40 response
2. To demonstrate that the efficacy of secukinumab 150 mg s.c., without loading, at Week 16 is superior to placebo based on the proportion of TNF naïve patients achieving an ASAS40 response
3. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the proportion of patients meeting the ASAS 5/6 response criteria
4. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the change from baseline in total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
5. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the proportion of patients achieving BASDAI 50
6. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the change from baseline of high sensitivity C-Reactive Protein (hsCRP)

7. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the change from baseline in total Bath Ankylosing Spondylitis Functional Index (BASFI)
8. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the change from screening in SI joint edema on MRI
9. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the proportion of subjects achieving an ASAS20 response
10. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the change from baseline in Short Form-36 Physical Component Summary (SF-36 PCS)
11. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) scores
12. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the proportion of patients achieving ASAS partial remission
13. Overall safety and tolerability of secukinumab

ANALYSIS PLAN B

1. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 52 is superior to placebo based on the proportion of all patients achieving an ASAS40 response
2. To demonstrate that the efficacy of secukinumab 150 mg s.c., with loading, at Week 52 is superior to placebo based on the proportion of TNF naïve patients achieving an ASAS40 response
3. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the proportion of subjects achieving an ASAS40 response
4. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the change from baseline in total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
5. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the proportion of patients achieving BASDAI 50
6. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 52 is superior to placebo based on the proportion of patients achieving BASDAI 50
7. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the change from baseline of high sensitivity C-Reactive Protein (hsCRP)
8. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the change from baseline in Short Form-36 Physical Component Summary (SF-36 PCS)

9. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) scores
10. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the proportion of patients meeting the ASAS 5/6 response criteria
11. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the proportion of subjects achieving an ASAS20 response
12. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the change from baseline in total Bath Ankylosing Spondylitis Functional Index (BASFI)
13. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 16 is superior to placebo based on the change from screening in SI joint edema on MRI
14. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 52 is superior to placebo based on the proportion of patients achieving Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-Reactive Protein (CRP) inactive disease as defined by ASDAS < 1.3
15. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 52 is superior to placebo based on the change from screening in SI joint edema on MRI
16. To demonstrate that the efficacy of secukinumab 150 mg s.c., with or without loading, at Week 52 is superior to placebo based on the change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) scores
17. Overall safety and tolerability of secukinumab



3 Investigational plan

3.1 Study design

This is a randomized, double-blind, placebo-controlled study. Approximately 555 analyzable patients will be randomized to one of three treatment groups (secukinumab 150 mg Load, secukinumab 150 mg No Load or placebo in a ratio of 1:1:1):

- **Group 1** (secukinumab 150 mg Load): secukinumab 150 mg (1 mL, 150 mg/mL) s.c. pre-filled syringe (PFS) at baseline (BSL), Weeks 1, 2 and 3, followed by administration every four weeks starting at Week 4
- **Group 2** (secukinumab 150 mg No Load): secukinumab 150 mg (1 mL, 150 mg/mL) s.c. PFS at BSL, placebo at Weeks 1, 2 and 3, followed by secukinumab 150 mg PFS administration every four weeks starting at Week 4
- **Group 3** (placebo): placebo (1 mL) s.c. PFS at BSL, Weeks 1, 2, 3, followed by administration every four weeks starting at Week 4

At Week 104, patients can continue in an optional randomized dose escalation treatment extension phase. The patients will be assessed based on their ASAS20 response at Week 104.

Secukinumab 150 mg responders at Week 104 (Core Phase Responders) will be randomized to the following treatment groups in a blinded manner:

- **Group 4** (Core Phase Responder 150 mg): secukinumab 150 mg (1 mL, 150 mg/mL) s.c. pre-filled syringe (PFS) and placebo (1 mL) s.c. PFS every four weeks

- **Group 5** (Core Phase Responder 300 mg): 2 injections with secukinumab 150 mg (1 mL, 150 mg/mL) s.c. PFS every four weeks

Secukinumab 150 mg incomplete-responders at Week 104 (Core Phase Non-Responders) will be escalated to secukinumab 300 mg in an open-label manner

- **Group 6** (Core Phase Non-Responder 300 mg): 2 injections with secukinumab 150 mg (1 mL, 150 mg/mL) s.c. PFS every four weeks open-label

Based on the clinical judgment of disease activity by the investigator and the patient, background medications, such as NSAIDs and DMARDs, may be modified or added to treat signs and symptoms of nr-axSpA **from Week 16 on**. Furthermore, patients who are repeatedly (e.g. at two or more consecutive visits) considered to be inadequate responders based on the clinical judgment of disease activity by the investigator and the patient, may receive secukinumab 150 mg s.c. or other biologics as standard of care treatment as outlined in Section 5.5.6 **from Week 20 on.**

Changes in concomitant medications used to treat nr-axSpA will not be allowed before the completion of all Week 16 assessments (see Section 5.5.6). Efficacy will be assessed in detail at every study visit, and patients who are deemed not to be benefiting from the study treatment based upon safety and efficacy assessments as defined in Section 5.5.9 or for any reason of their own accord will be free to discontinue participation in the study at any time.

Patients will be stratified at randomization according to the subgroup of objective signs of inflammation they belong to (based on their CRP and MRI status at screening). The only condition that will be placed on enrollment is that no less than 15% of patients should belong to either of the three subgroups of objective signs of inflammation: CRP+ **and** MRI+, CRP+ **and** MRI-, CRP- **and** MRI+.

Additionally, it is planned to enroll no more than approximately 20% TNF-IR patients in the study. Due to the long wash out required for some TNF-IR patients, enrolment of TNF-IR patients will end two months prior to the projected end of screening period.

Starting at Week 52, all patients will be assigned to receive secukinumab 150 mg s.c. in an open-label fashion except for those patients who discontinued blinded study treatment (secukinumab 150 mg or placebo) during the initial 52 weeks of the study.

The originally randomized treatment assignment (secukinumab 150 mg or placebo) will remain blinded until all patients have completed the Week 52 visit. After all patients have completed the Treatment Period 2 (Week 52) and the Week 52 database lock has occurred, site personnel and patients may be unblinded to the original randomized treatment assignment at baseline. All patients will continue to receive secukinumab as open-label treatment up to Week 100, unless they have discontinued study treatment.

Starting at Week 104, all patients who finish the core phase according to the protocol on study medication will be asked to continue in an additional extension phase. A new Informed Consent form has to be signed before proceeding into the extension phase. The patients will be assessed as having been Core Phase Responders (i.e., achieving ASAS20 at Week 104) or Core Phase Non-Responders (i.e., not achieving ASAS20 at Week 104). Core Phase Responders will be randomized 1:1 to continue on secukinumab 150 mg or escalated to 300 mg treatment. Core Phase Non-Responders will receive 300 mg treatment open-label.

At the end of the 16-week dose escalation treatment period, all patients will continue on their current treatment until the last patient has finished the 16-week dose escalation treatment period (i.e., continuous treatment period).

Starting from Week 156 onward, a patient can be up-titrated to secukinumab 300 mg open-label based on the clinical judgment of disease activity by the investigator. The original dose of the extension phase will only be unblinded on an individual patient level at the end of the extension phase for each patient to enable continuous treatment on the same dose, if available.

A follow-up visit is to be done 12 weeks after last administration of study treatment for all patients, regardless of whether they complete the entire study (either core or extension phase) as planned or discontinue prematurely.

Subjects who complete the 2- year Core Phase are eligible to enter the extension phase.

Figure 3-1 Study design Core Phase

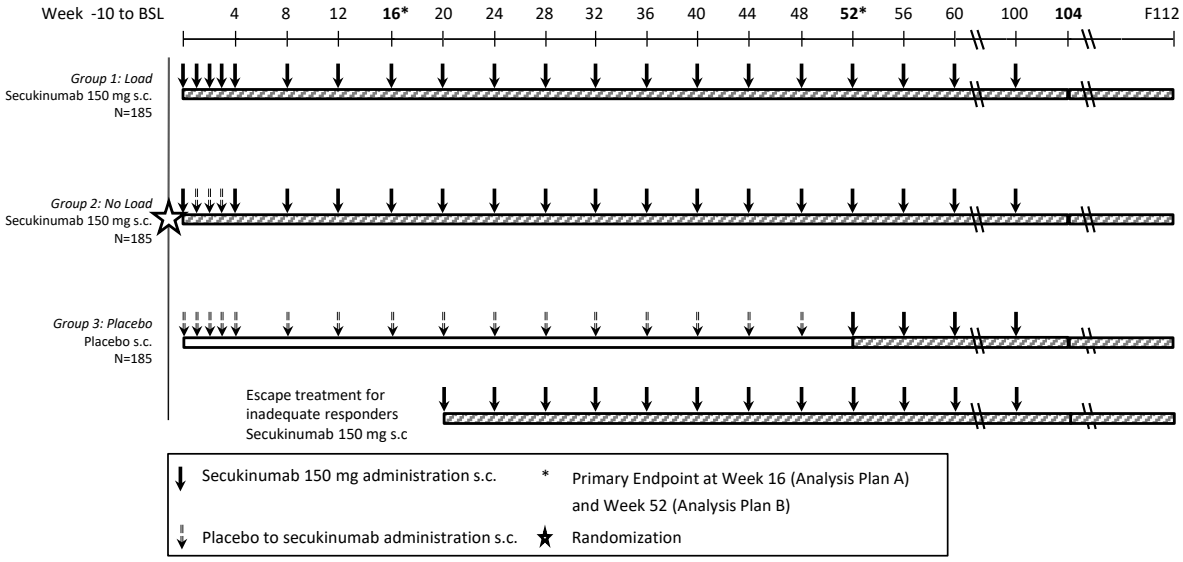
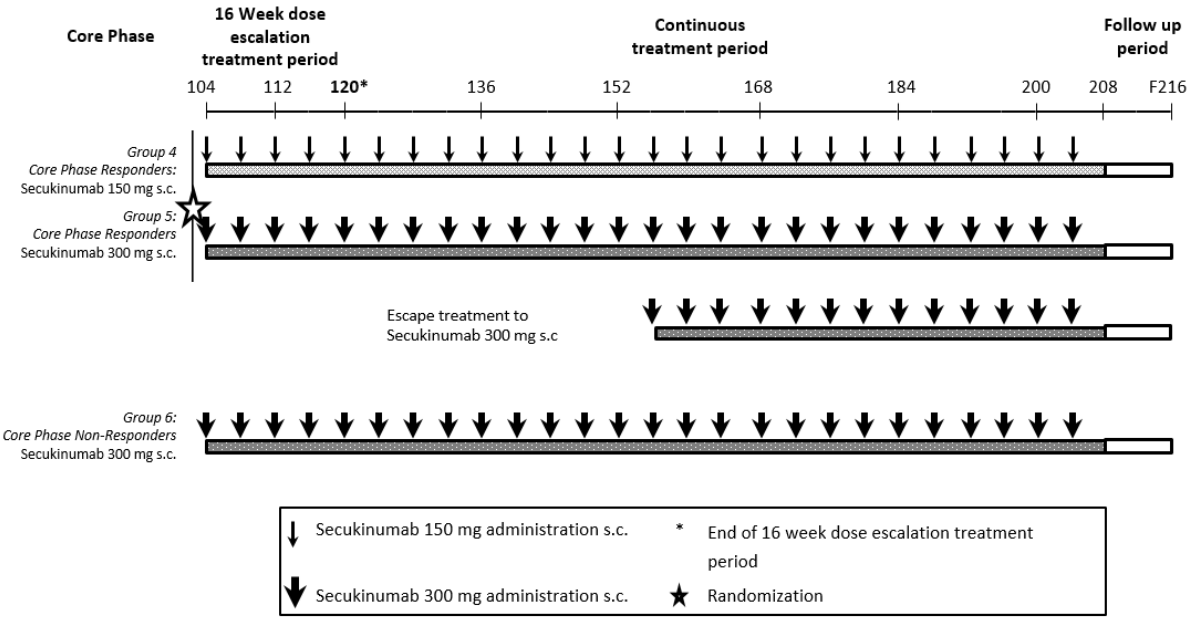


Figure 3-2 Study design Extension Phase



3.2 Rationale of study design

This phase III trial utilizes a double-blind, randomized, placebo-controlled design with two different loading regimens. The treatment duration of the placebo group will be 52 weeks. Starting at Week 20, all patients who are repeatedly (e.g. two or more consecutive visits) considered to be inadequate responders based on the clinical judgment of disease activity by the investigator and /or the patient will receive secukinumab 150 mg s.c. or can switch to standard of care after observing the required wash out period as described in Section 5.5.6. This is in compliance with the EMA/EMEA (European Medicines Agency) guidelines for AS (EMA 2009), considered relevant for trials in nr-axSpA and in line with guidance provided by the FDA. All other patients will continue their original randomly assigned treatment. From Week 52 on, all patients will receive secukinumab 150 mg every 4 weeks up to Week 100 unless they have discontinued study treatment.

All patients can join the extension phase upon completing the core phase of the study. During the first 16 weeks of the extension phase, it will be assessed if a higher dose of treatment (secukinumab 300 mg) will provide further benefit to patients. The 300 mg dose is an approved dose for secukinumab in psoriasis as well as psoriatic arthritis. At the end of the 16-week randomized escalation treatment phase, the patients will continue on their current treatment for a maximum duration of an additional 2 years after the end of the core phase. However, the study will end once the last patient has finished the 16-week dose escalation treatment phase.

After the first year of the extension phase, the study medication can be escalated to 300 mg s.c. every 4 weeks open-label for patients whose overall therapeutic response is not fully achieved with the current dose and may improve with a higher dose, as judged by the investigator. The decision to escalate the study medication may be determined at any site visit after the first year of the extension phase. For patients escalated to 300 mg open-label, no dose reduction can be performed at a later time point.

Regular assessments of disease activity ensure that patients who are experiencing worsening of disease in any of the treatment groups can be discontinued from the study as described in Section 5.5.9.1. Data up to 216 weeks (204 weeks of treatment plus 12 weeks of safety follow-up) is being generated to evaluate the safety and the duration of response in this population.

3.3 Rationale of dose/regimen, route of administration and duration of treatment

The dosing regimen in this study is based upon dose-efficacy relationships observed in a proof of concept (PoC) trial (CAIN457A2209) and two phase III trials (CAIN457F2305, CAIN457F2310) in AS. The Phase III trials in AS, CAIN457F2305 and CAIN457F2310, assessed the efficacy of both 75 mg and 150 mg s.c. maintenance doses with loading regimens consisting of either intravenous doses (CAIN457F2305: 3 doses of 10 mg/kg given every 2 weeks at BSL, Weeks 2 and 4) or subcutaneous doses (CAIN457F2310: 4 weekly doses matching the maintenance dose of either 75 mg or 150 mg given at BSL, Weeks 1, 2, and 3). Given the similarity of the ASAS20 and ASAS 40 response at the Week 16 primary endpoint for the 150 mg dose in each of these studies, regardless of whether the loading dosing was i.v. (CAIN457F2305: 60.8% for IV-150 mg vs 28.7% for placebo for ASAS20 and 41.6% for IV-150 mg vs 13.1% for placebo for ASAS 40) or s.c. (CAIN457F2310: 61.1% for SC-150 mg vs 27.0% for placebo for ASAS20 and 36.1% for SC-150 mg vs 10.8% for placebo for ASAS 40), secukinumab 150 mg s.c. is a sufficient dose to provide clinically and statistically significant efficacy, whereas higher loading doses of secukinumab do not appear to confer greater efficacy in AS. Of note, the 75 mg s.c. loading and maintenance regimen tested in CAIN457F2310 did not achieve statistically significant improvements in any of the efficacy endpoints tested in a pre-defined testing hierarchy, including ASAS20, ASAS 40, hsCRP, ASAS5/6, BASDAI, SF-36 PCS and ASQoL. Therefore, there are currently no plans to further pursue the 75 mg dose in future studies. Furthermore, a meta-analysis of trials examining TNF-α inhibitors, demonstrated that nr-axSpA patients respond similarly well to biologic anti-TNF treatments as AS patients (Callhoff et al 2014). There was no evidence that different axSpA populations (e.g. AS and nr-axSpA) could require different dose regimens (Callhoff et al 2014, Landewe et al 2014). As other phase III trials of TNF-α inhibitors in nr-axSpA also evaluated dosages that already proved to be efficacious in AS, this trial will use the secukinumab dose of 150 mg s.c.

In addition to evaluating the 150 mg s.c. loading and maintenance regimen for efficacy compared with placebo, this study will also assess the impact of the s.c. loading regimen itself on efficacy by including a treatment arm of 150 mg maintenance dosing without a s.c. loading regimen. Thus, the loading regimen (150 mg Load) will assess initial weekly administration of 150 mg for 4 weeks (BSL, Weeks 1, 2, and 3) followed by maintenance dosing every 4 weeks at the same dose starting at Week 4, whereas the No Load regimen will assess dosing of 150 mg given every 4 weeks from BSL onward, with placebo dosing given during the loading phase to mask the two active treatment regimens. Both secukinumab regimens will be compared to a placebo arm whose dosing simulates the loading regimen, in order to blind placebo treatment compared to either active treatment arm.

Notably, 300 mg s.c. administered monthly is an approved dose for secukinumab in both psoriasis and in PsA, and the safety profile for 300 mg s.c. every 4 weeks is comparable to 150 mg s.c. every 4 weeks (Langley et al, 2014, McInnes et al, 2015). The higher dose of

secukinumab confers an additional benefit in other disease conditions (e.g., psoriasis and PsA). This study will evaluate whether a higher dose of secukinumab will have an effect on subjects with nr-axSpA with respect to treatment response. The dose escalation will be done in a randomized and blinded manner for responding patients who achieve an ASAS20 response at the end of the core phase, whereas non-responders will all be escalated during the extension phase in open-label fashion to the 300 mg dose. This will allow an assessment of the effect of 150 mg and 300 mg in an unbiased manner, as no study has yet assessed both 150 mg or 300 mg s.c. in nr-axSpA.

After the first year of randomized treatment in the extension phase, patients whose overall therapeutic response is not fully achieved with the current dose and may improve with a higher dose, as judged by the investigator, can escape to the open-label 300 mg dose.

3.4 Rationale for choice of comparator

A placebo arm up to Week 52 is included in this study. Due to the nature of the disease and the outcome measures used (e.g., ASAS response criteria, MRI for inflammation), a placebo arm is necessary to obtain reliable efficacy measurements. As there is currently conflicting evidence as to whether biologic treatments for axSpA are able to slow down or halt the structural progression of the disease, there is a need to study whether secukinumab as a new treatment option targeting IL-17A has a positive effect on correlates of structural damage evident on MRI of the sacroiliac joint (SIJ) and the spine as compared to placebo. A placebo controlled period of one year is considered the shortest possible timeframe to assess differences in effects on signs of structural damage (assessed by MRI) between both treatment groups. In a similar population, the anti-TNF α agent etanercept failed to show a reduction or a stop in progression of fatty lesions over 1 year of treatment compared to sulfasalazine (Song et al 2011). The continuation of the placebo group up to Week 52 can be supported from an ethical standpoint, as patients continue their treatment with NSAIDs and other concomitant treatments including MTX and sulfasalazine. If the patient or investigator feels the level of disease activity requires an escalation in therapy, background medications such as NSAIDs and DMARDs may be modified or added after Week 16, and all patients repeatedly (e.g. two or more consecutive visits) considered to be not responding to treatment can be re-assigned to secukinumab 150 mg or standard of care from Week 20 on as described in Section 3.2. Moreover, the inclusion of a placebo group is in accordance with previously implemented methodology and in compliance with the EMA/EMEA (European Medicines Agency) guidelines for AS (EMA 2009), considered relevant for trials in nr-axSpA and recommended by the FDA.

3.5 Purpose and timing of interim analyses/design adaptations

The first primary endpoint analysis will be performed after all patients complete the treatment period 1 of the study (Week 24 for analysis plan A) and again after all patients complete the treatment period 2 of the study (Week 52 for analysis plan B).

Depending on health authority advice, group sequential testing, as described in the statistical analysis plan, might be done at the Week 24 interim analysis for the Week 52 timepoint. The final analysis of the core phase will be conducted after all patients complete the Week 104 study visit.

The final analysis of the treatment escalation phase will be conducted after the last patient has completed the 16-week dose escalation treatment period and the required follow-up period of 12 weeks after the last study dose.

Although unblinding will occur after the Week 24 database lock, the original randomization to active treatment vs placebo will continue to remain blinded to all investigators, site personnel and patients until all patients have completed the treatment period 2 (Week 52) and the Week 52 database lock has occurred. If required by health authorities, a separate study team will conduct the 24 Week interim analysis and no access to the interim results or individual treatment assignments will be given to the study team conducting the ongoing trial until the Week 52 database lock.

3.6 Risks and benefits

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

As of July 2015, approximately 12000 subjects have been enrolled in both completed and ongoing studies with secukinumab, with over 9600 having received active drug at doses ranging from single and/or multiple doses of 0.1 mg/kg to 30 mg/kg i.v. and 25 mg to 300 mg s.c. across various indications (including psoriasis, RA, AS, PsA, multiple sclerosis and uveitis).

The risk profile of secukinumab in nr-axSpA is informed by the safety experience from psoriasis and arthritides trials. Secukinumab has been studied most extensively in psoriasis, and side effects seen in psoriasis patients treated with secukinumab include upper respiratory tract infections (nasopharyngitis, rhinitis) (very common: in more than 1 in 10 patients); oral herpes, rhinorrhea, diarrhea and urticaria (common: in more than 1 in 100 but fewer than 1 in 10 patients); oral candidiasis, tinea pedis, neutropenia, and conjunctivitis (uncommon: in more than 1 in 1,000 but fewer than 1 in 100 patients). Additionally, worsening of Crohn's disease, in some cases serious, was seen in studies of Crohn's disease and psoriasis, in patients receiving secukinumab or placebo.

In the phase III AS studies CAIN457F2305 and CAIN457F2310 in 590 patients the most common side effects in the 52-week dataset were upper respiratory tract infection, nasopharyngitis, pharyngitis and oral herpes as secukinumab treatment-related adverse events which generally were mild to moderate in severity and did not lead to study drug discontinuation.

Immunogenicity was low with secukinumab and did not correlate with hypersensitivity-related adverse event or loss of efficacy in all indications studied up to date.

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

4 Population

The study population will consist of male and female patients (≥ 18 years old at the time of consent) fulfilling the ASAS classification criteria for axSpA plus an abnormal CRP and/or

MRI, with no radiographic evidence of changes in the sacroiliac joints that would meet the modified New York criteria for AS (described in Appendix 3).

Patients included must report active disease despite current or previous NSAID, non-biologic DMARD, and/or anti-TNFα therapy. Patients should have been on NSAIDs at the highest recommended dose for at least 4 weeks in total prior to randomization with an inadequate response or failure to respond, or less than 4 weeks if therapy had to be withdrawn due to intolerance, toxicity or contraindications. Patients who have been on a TNFα inhibitor (not more than one) must have experienced an inadequate response to treatment given at an approved dose for at least 3 months prior to randomization or have been intolerant to at least one administration of an anti-TNFα agent. It is planned to limit the inclusion of patients that are TNF inadequate responders (TNF-IR) to no more than 20% of the overall randomized population. Due to the long wash out required for some TNF-IR patients, enrolment of TNF-IR patients will end two months prior to the projected end of screening period.

The study aims to randomize approximately 555 analyzable patients worldwide. Enrollment will stop as soon as the target number of randomized analyzable patients is reached.

Patients can be re-screened only once, and no study-related re-screening procedure should be performed prior to written re-consent by the patient. Mis-randomization occurs when a patient who does not meet all eligibility criteria receives a randomization number nevertheless; mis-randomized patients will not be re-screened.

4.1 Inclusion criteria

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

1. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study assessment is performed
2. Male or non-pregnant, non-nursing female patients at least 18 years of age
3. Diagnosis of axSpA according to ASAS axSpA criteria (Appendix 4):
   a. Inflammatory back pain for at least 6 months
   b. Onset before 45 years of age
   c. Sacroiliitis on MRI with ≥ 1 SpA feature OR HLA-B-27 positive with ≥2 SpA features
4. Objective signs of inflammation **at screening**, evident by either
   - MRI with Sacroiliac Joint inflammation (Appendix 6)
     AND / OR
   - hsCRP > ULN (as defined by the central lab)
5. Active axSpA as assessed by total BASDAI ≥ 4 cm (0-10 cm) **at baseline**
6. Spinal pain as measured by BASDAI question #2 ≥ 4 cm (0-10 cm) **at baseline**
7. Total back pain as measured by VAS ≥ 40 mm (0-100 mm) **at baseline**
8. Patients should have been on at least 2 different NSAIDs at the highest recommended dose for at least 4 weeks in total prior to randomization with an inadequate response or failure to respond, or less if therapy had to be withdrawn due to intolerance, toxicity or contraindications

9. Patients who are regularly taking NSAIDs (including COX-1 or COX-2 inhibitors) as part of their axSpA therapy are required to be on a stable dose for at least 2 weeks before randomization
10. Patients who have been on a TNFα inhibitor (not more than one) must have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months prior to randomization or have been intolerant to at least one administration of an anti-TNFα agent
11. Patients who have previously been on a TNFα inhibitor will be allowed entry into study after an appropriate wash-out period prior to randomization:
    - 4 weeks for Enbrel® (etanercept) – with a terminal half-life of 102 ± 30 hours (s.c. route)
    - 8 weeks for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (i.v. infusion)
    - 10 weeks for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route)
    - 10 weeks for Simponi® (golimumab) – with a terminal half-life of 11-14 days
    - 10 weeks for Cimzia® (certolizumab) – with a terminal half-life of 14 days
12. Patients taking 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
13. Patients on MTX must be on stable folic acid supplementation before randomization
14. Patients who are on a DMARD other than MTX or sulfasalazine must discontinue the DMARD 4 weeks prior to randomization, except for leflunomide, which has to be discontinued for 8 weeks prior to randomization unless a cholestyramine washout has been performed
15. Patients taking systemic corticosteroids have to be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization.

Inclusion criteria for extension phase:

1. Written informed consent must be obtained before any assessment is performed.
2. Patients who have completed the full study treatment period (104 weeks) in the core phase on study treatment.

4.2 Exclusion criteria

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

1. Patients with radiographic evidence for sacroiliitis, grade ≥ 2 bilaterally or grade ≥ 3 unilaterally (radiological criterion according to the modified New York diagnostic criteria for AS; Appendix 3) as assessed by central reader
2. Inability or unwillingness to undergo MRI (e.g., patients with pacemakers, aneurysm clips or metal fragments / foreign objects in the eyes, skin or body that are not MRI compatible)

3. 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
4. Patients taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine)
5. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor
6. Use of any investigational drug and/or devices within 4 weeks of randomization, or a period of 5 half-lives of the investigational drug, whichever is longer
7. History of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes
8. Any therapy by intra-articular injections (e.g., corticosteroid) within 4 weeks before randomization
9. Any intramuscular corticosteroid injection within 2 weeks before randomization
10. Patients previously treated with any biological immunomodulating agents, except those targeting TNFα
11. Patients who have taken more than one anti-TNFα agent
12. 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)
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 human chorionic gonadotropin (hCG) laboratory test
14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during entire study or longer if required by locally approved prescribing information (e.g. 20 weeks in EU). Effective contraception methods include:
    - Total abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 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 patients on the study, the vasectomized male partner should be the sole partner for that patient
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
    - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
    - Placement of an intrauterine device or intrauterine system

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

Women are considered post-menopausal 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 ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

15. Active ongoing inflammatory diseases other than axSpA that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease or uveitis
16. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions, which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy
17. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥ 160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV), uncontrolled diabetes, or very poor functional status unable to perform self-care
18. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria:
    - Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out lab error.
    - If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.
19. 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)
20. 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)
21. Active systemic infections during the last two weeks prior to randomization (exception: common cold)
22. 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 6-1. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment according to local country guidelines must have been initiated
23. Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening or randomization

24. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)
25. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial
26. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)
27. Inability or unwillingness to receive injections with PFS
28. 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
29. Donation or loss of 400 mL or more of blood within 8 weeks before dosing
30. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization
31. Plans for administration of live vaccines during the study period or 6 weeks prior to randomization

Exclusion criteria for extension phase:

No additional exclusion criteria apply for the extension phase

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Novartis/CRO will supply the following study treatments:

- Investigational Treatment:
  - Secukinumab 150 mg provided in a 1 mL PFS (one PFS for 150 mg dose)
- Reference Therapy:
  - Secukinumab placebo (Placebo) provided in a 1 mL PFS

After the Week 24 database lock, the Sponsor will be unblinded to treatment assignment in order to perform the first primary efficacy analysis. Although unblinding will occur after the Week 24 database lock, the original randomization to active treatment vs placebo will continue to remain blinded to all investigators, site personnel and patients until all patients have completed the treatment period 2 (Week 52) and the week 52 database lock has occurred. If required by health authorities a separate study team will conduct the 24 week interim analysis and no access to the interim data will be given to the study team conducting the ongoing trial until Week 52. After the treatment period 2 (Week 52) has been completed for all patients and the Week 52 database lock has occurred, the site personnel, patients and study team directly involved with the conduct of the trial may be unblinded to the randomized treatment assignment

at baseline. From Week 52 onwards, all patients regardless of efficacy response will receive open-label secukinumab 150 mg s.c. unless they have discontinued study treatment.

After the core phase of the study, patients can join the extension phase and will receive either double-blinded or open-label treatment consisting of two injections per treatment.

Patients will be instructed by site staff on how to self-administer the s.c. injection using the PFS containing the liquid formulation of secukinumab/placebo, based on the Instructions for Use (IFU). The s.c. investigational drug will be administered by the patient into the appropriate injection site of the body under the supervision of the site staff.

Note: The Secukinumab/Placebo PFSs are packaged in double-blinded fashion until Week 52 when open-label treatment is started and, therefore, do not need to be prepared by the study site. Starting at Week 52, open-label medication will be supplied until the last dose is given at Week 100.

In the extension phase, the study medication will again be provided in a double-blinded fashion to mask the 150 mg and 300 mg doses.

The core phase medication will be labeled as follows:

- Double-blind Secukinumab and Placebo PFS will be labeled as AIN457 150mg/1mL/Placebo.
- Open-label Secukinumab PFS will be labeled as AIN457 150mg/1mL

The extension study medication will be labeled as follows:

- Double-blind Secukinumab and Placebo PFS will be labeled as AIN457 150mg/1mL/Placebo.
- Open-label Secukinumab PFS will be labeled as AIN457 150mg/1mL

For detailed instructions on storage of the investigational treatments, please refer to Section 5.5.3.

5.1.2 Additional study treatment

No additional treatment beyond investigational treatment is required for this trial.

5.2 Treatment arms

Patients will be assigned to one of the following three treatment arms in a 1:1:1 ratio, with approximately 185 analyzable patients each in the following arms:

- Group 1: Secukinumab 150 mg Load
- Group 2: Secukinumab 150 mg No Load
- Group 3: Placebo

Patients will receive study treatment at BSL, Weeks 1, 2, 3, and 4 followed by treatment every 4 weeks through Week 100. Patients who are repeatedly (e.g. two or more consecutive visits) considered to be inadequate responders based on the clinical judgement of disease activity from Week 20 on, can receive secukinumab 150 mg s.c. or standard of care treatment as outlined in Section 5.5.6. In case the chosen standard of care is a TNFα inhibitor, a 12-week wash-out period has to be observed.

After Week 52 database lock, all patients will receive secukinumab 150 mg s.c. in open-label fashion, without a loading regimen for patients switching from placebo, unless they have discontinued study treatment. Blinding to the original treatment assignment will be maintained until the treatment period 2 (Week 52) is completed by all patients. Patients will self-administer all secukinumab and placebo doses as described in Section 3.1 at the study site or at home, according to the assessment schedule in Table 6-1.

Patients in the extension phase will be assigned to one of the following three treatment arms:

Core Phase Responders:

- Group 4: Secukinumab 150 mg blinded
- Group 5: Secukinumab 300 mg blinded

Core Phase Non-Responders:

- Group 6: Secukinumab 300 mg open-label

At Week 104, patients will be assessed as being Core Phase Responders or Core Phase Non-Responders. Core Phase Responders will be randomized to treatment group 4 or 5; Core Phase Non-Responders will receive treatment according to group 6. Patients will self-administer all secukinumab and placebo doses as described in Section 3.1 at the study site or at home, according to the assessment schedule in Table 6-2. After the first year in the extension phase (Week 156), patients whose overall therapeutic response is not fully achieved with the current dose and may improve with a higher dose, as judged by the investigator, can escape to open-label secukinumab 300 mg. The study will remain blinded until the randomized 16-week extension period for the last patient is completed and the database is locked after the completion of all follow-up visits.

5.3 Treatment assignment, randomization

At baseline, all eligible patients will be randomized to one of the treatment arms via Interactive Response Technology (IRT). The investigator or delegate will contact the IRT system after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the patient.

From Week 20 on, the patient's responder status (responder / inadequate responder) which should be based on the clinical judgment of disease activity should be entered into IRT. Patients repeatedly (e.g. two or more consecutive visits) considered to be inadequate responders may receive secukinumab 150 mg or standard of care as outlined in Section 5.5.6. Starting at Week 52, all patients will receive secukinumab 150 mg up to Week 104 with last study treatment administered at Week 100, unless they have discontinued study treatment.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient 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

Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Patients will be stratified at randomization according to the subgroup of objective signs of inflammation they belong to (based on their CRP and MRI status at screening). The only condition that will be placed on enrollment is that no less than 15% of patients should belong to either of the three subgroups of objective signs of inflammation: CRP+ **and** MRI+, CRP+ **and** MRI-, CRP- **and** MRI+.

Additionally, it is planned to enroll no more than 20% TNF-IR patients in the study.

At the beginning of the extension phase, patients will be assessed as being Core Phase Responders or Core Phase Non-Responders at Week 104 based on ASAS20 response. Core Phase Responders will be randomized via IRT. The investigator or delegate will contact the IRT system after confirming that the patient fulfills the inclusion criteria for the extension phase. The randomization number of the patient will remain the same as assigned in the core phase, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the patient in the extension phase. Core Phase Non-Responders will be recorded in IRT as a non-responder and will receive open-label treatment with secukinumab 300 mg s.c.

From Week 156 onward, patients whose overall therapeutic response is not fully achieved with the current dose and may improve with a higher dose, as judged by the investigator, can escape to open-label secukinumab 300 mg.

The randomization scheme for patients will be reviewed and approved by a member of the IQS Randomization Group.

5.4 Treatment blinding

This is a double-blind randomized treatment trial. Although unblinding will occur after the Week 24 database lock, the original randomization to active treatment vs placebo will continue to remain blinded to all investigators, site personnel and patients until all patients have completed the treatment period 2 (Week 52) and the Week 52 database lock has occurred. If required by health authorities, a separate study team will conduct the 24 Week interim analysis and no access to the interim data will be given to the study team conducting the ongoing trial until Week 52. The blind is kept by 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 except the bioanalyst; (2) The identity of the original randomized treatments administered through Week 52 will be concealed up to the Week 52 by the use of study treatments in the form of PFS for s.c. injection, filled with secukinumab or placebo that are identical in appearance during the double-blind treatment period. Analysis results for any interim study reports generated prior to unblinding that would reveal subject-level data will be kept in a secured area.

[redacted]

The hsCRP results from samples collected during the treatment period will be revealed only after all patients have completed the treatment period 2 (Week 52). For details regarding the planned Interim Analyses, refer to Section 3.5.

The reading of MRI and X-ray will be performed in a blinded fashion by independent readers and post screening results will only be provided to the sites after full unblinding of the study.

Other unblinding of original randomized treatment assignment before Week 52 will only occur in the case of patient emergencies (see Section 5.5.12) and at the conclusion of the study.

The extension phase will be conducted in double-blinded fashion (for Core Phase Responders) and will remain blinded for the duration of each individual patient's participation in the study. At the end of the extension treatment phase, which may last up to 2 years for any individual patient, investigators can request single-patient unblinding to support continuous treatment of the respective patient at their study-provided dose of secukinumab, if available.

5.5 Treating the patient

5.5.1 Patient numbering

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

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

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

All patients will continue in the extension phase with their original subject number assigned for the core phase.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with investigational treatment in packaging of identical appearance.

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

After Week 52, if the patient opts for home administration (at protocol specified time points, see Table 6-1 and Table 6-2) the investigator will dispense, via IRT, an appropriate number of investigational treatment packages for home administrations. The investigator will detach the outer part of the label and affix it to the source documentation (Drug Label Form). Detailed instructions on the self-administration of the study treatment will be described in the IFU provided to each patient and made available to the site staff and investigator. These instructions should be reviewed in detail by the patient and the site personnel.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. The investigator should educate the patient on how to properly store the study treatment if the patient is self-administering at home.

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

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

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

5.5.3.2 Handling of other study treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Study treatment (150 mg secukinumab and placebo) will be administered s.c. by 1 mL PFS throughout the study as 150 mg / 1 mL secukinumab or 1 mL placebo, respectively. Administration of study treatment will occur via self-injection at the study site through Week 52. Administration of study treatment must occur after the study assessments for the visit have been completed. The PFS with the ready-to-use study treatment solution will be provided by the site staff to the patient. Detailed instructions on the self-administration of the study treatment will be described in the IFU for secukinumab and provided to each patient. After Week 52, patients will be allowed to self-administer the study treatment at home during the optional visits in which there are no scheduled assessments at the site (see Table 6-1 and Table 6-2 below). If

the patient is not comfortable self-injecting the study treatment, then the site staff or caregiver can administer it for the patient.

At the BSL visit, patients will be instructed by the site staff, utilizing the IFU, on how to self-inject using a PFS. Patients will be asked to raise any questions and then to proceed with self-injection. At the Week 1 visit, patients will be asked to refer to the IFU and to proceed directly with self-injection of the study drug (i.e., no prior retraining) for the remainder of the trial. However, if the patient is not comfortable self-injecting the study treatment, then the site staff may administer it for the patient.

All study treatment kits assigned to the patient during the study will be recorded in the IRT.

[redacted]

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

Home administration

Up to Week 52, all doses of study treatment will be self-administered by the patient at the study site, after the study assessments for the visit have been completed. After Week 52, the patients will be allowed to self-administer the study treatment at home during the optional visits in which there are no scheduled site assessments. Optional site visits are included in the assessment table of the study (Table 6-1), between visits in which trial-related procedures are to be conducted. Patients will be allowed to self-administer the study treatment by PFS at home or to visit the site during the optional visits to self-administer study treatment under the supervision of the site staff. If the patient opts for home administration of study treatment and is unable or unwilling to self-administer the treatment via PFS, a caregiver may administer the study treatment after Week 52. Caregivers should be trained on the IFU prior to administering the study treatment to the patient. It should be recorded on the Dose Administration Record eCRF(s) whether the patient self-administered the study treatment at home or at the site and if a caregiver administered the treatment**.** In the extension phase of the study, the optional site visits for drug administration will continue to be possible, but will only be recorded in the source documents at the site.

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

All dates and times of self-administrations by the patient during the study must be recorded on the Dosage Administration Record eCRF. Immediately before dispensing the package to the patient, site staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.5 Permitted dose adjustments and interruptions of study treatment

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

Study treatment interruption is only permitted if, in the opinion of the investigator, a patient is deemed to be at a significant safety risk unless administration of investigational treatment is temporarily interrupted. In such cases study treatment should be interrupted only during the time that this risk is present and ongoing. Study treatment can be restarted at the next scheduled visit after resolution of the safety risk.

The effect of secukinumab on live vaccines is unknown; therefore live vaccines should not be administered during participation in the study. In case a live vaccine has been administered due to a medical urgency, study treatment should be interrupted for 12 weeks.

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

5.5.6 Allowed treatment modifications and escape treatment

Treatment modifications as new therapeutic interventions or a significant change to ongoing therapy must not be made before completion of Week 16 assessments.

From Week 16 on, if the patient or investigator feels the level of disease activity requires an escalation in therapy, background medications such as NSAIDs and DMARDs may be modified or added to treat signs and symptoms of nr-axSpA as outlined in Section 5.5.7. All medication changes must be recorded in the eCRF page.

From Week 20 on, based on the clinical judgment of disease activity by the investigator and the patient, patients may be considered as inadequate responders. Patients who are repeatedly (e.g. two or more consecutive visits) considered to be inadequate responders will have the option to enter escape. Upon entering "escape", patients have the option (at investigator/patient discretion) to continue to receive blinded study treatment or switch to open-label locally applicable standard of care. Patients continuing with blinded study treatment will be assigned to receive secukinumab 150 mg s.c. (patients originally assigned to placebo) or continue to receive secukinumab 150 mg s.c. (patients originally assigned to secukinumab). While the standard of care will be open-label, the originally randomized treatment assignment (secukinumab 150 mg or placebo) will remain blinded. If the standard of care includes the use of a biologic such as a TNFα inhibitor, it should be prescribed in accordance with investigator practice and local treatment guidelines. Patients switching to a biologic therapy (e.g. anti-TNF) other than secukinumab must not receive any further study medication and will have to observe a 12 week wash out period after the last application of study treatment prior to starting any other biologic treatment. The earliest time point for a patient to receive a biologic as standard of care would thus be at Week 28. All other patients will continue their original randomly assigned treatment.

From Week 156 onward, patients whose overall therapeutic response is not fully achieved with the current dose and may improve with a higher dose, as judged by the investigator, can escape to open-label secukinumab 300 mg.

While nr-axSpA is a multifaceted disease and the assessment of responder status should be based on the global clinical picture and not on a single efficacy parameter; repeatedly (e.g. at two or more consecutive visits) not achieving a clinically meaningful improvement in the BASDAI of ≥ 20% or ≥ 1 unit (0 – 10 scale) (Pavy et al. 2005) may be considered as a general guidance for considering a patient inadequate responder to study treatment.

Although no patient will be restricted from receiving necessary medications for lack of benefit or worsening of disease, if treatment with prohibited biologics (as described in Section 5.5.8) occurs, patients may remain in the trial but must discontinue study treatment. Efficacy will be assessed in detail at every study visit, and patients who are deemed not to be benefiting from the study treatment based on safety and efficacy assessments (see Section 5.5.9) or for any reason on their own accord will be free to discontinue participation in the study at any time. Changes in NSAID, non-biologic DMARDs and corticosteroid concomitant therapy are permitted as per investigator's and patient's clinical judgment after all Week 16 assessments are completed. Please see Section 5.5.7, Section 5.5.8 and Section 5.5.9 for details.

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

5.5.7 Concomitant treatment

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

Guidelines for the use of specific medications are provided below:

Methotrexate

Patients taking MTX (≤ 25 mg/week) must be on a stable dose for at least 4 weeks before randomization and maintained stable until Week 16. Any changes in dose or initiation after Week 16 must be recorded in the Prior/Concomitant medications eCRF page.

Folic acid

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

Sulfasalazine

Patients taking sulfasalazine (≤ 3 g/day) must be on a stable dose for at least 4 weeks before randomization and maintained stable until Week 16. Any changes in dose or initiation after Week 16 must be recorded in the Prior/Concomitant medications eCRF page.

Leflunomide wash-out with cholestyramine

In case of leflunomide treatment, a drug wash-out of 8 weeks has to be performed. However, another wash-out procedure might 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 patients who require a drug elimination procedure. If a patient receives the dose of 8 g t.i.d. for 11 days, he/she could be safely randomized 4 weeks after the beginning of the 11 days treatment period.

After all Week 16 assessments are completed, leflunomide therapy may be initiated as a background medication. Any initiation or changes in dose after Week 16 must be recorded in the Prior/Concomitant medications eCRF page.

Systemic corticosteroids

Treatment with systemic corticosteroids is permitted if the dose was stable within the 2 weeks preceding randomization, up to a maximum daily dosage of 10 mg prednisone equivalent. After Week 16, the dose and regimen of systemic corticosteroids may be modified as per investigator's judgment and patient's need, although the corticosteroid dose should not be reduced rapidly. 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. 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) and acetaminophen/paracetamol

Patients 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.

NSAIDs, low strength opioids or paracetamol/acetaminophen PRN can be taken during the study; however, patients should refrain from any intake during at least the 24 hours before a visit with disease activity assessment.

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.

TNFα inhibitors

If TNFα inhibitors are chosen as escape treatment for patients considered as inadequate responders, a 12 weeks wash out period has to be observed after administration of the last dose of blinded study treatment for safety reasons. Thus, the earliest time for the patient to receive the TNFα inhibitor will be at Week 28. Initiation of TNFα inhibitors must be recorded on the corresponding eCRF page.

TNFα inhibitors prescribed in accordance with investigator practice, treatment guidelines or locally approved uses will not be considered study medication and will not be supplied by the sponsor.

5.5.8 Prohibited Treatment

Use of the treatments displayed in Table 5-1 is NOT allowed after the start of the washout period unless otherwise specified below. Treatment continuation with secukinumab at the end of the treatment phase is acceptable.

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

Table 5-1 Prohibited treatment

Prohibited treatments	Washout period (before randomization)
Etanercept* (until Week 28, if used as escape treatment)	4 weeks
Infliximab* (until Week 28, if used as escape treatment)	8 weeks
Adalimumab, golimumab, certolizumab* (until Week 28, if used as escape treatment)	10 weeks
Unstable dose of MTX or sulfasalazine (until Week 16)	4 weeks
Other DMARD (except MTX or sulfasalazine) (until Week 16)	4 weeks
Leflunomide (until Week 16)	8 weeks
Leflunomide with Cholestyramine washout	4 weeks
Unstable dose of NSAIDs (COX1 or COX2 inhibitors) (until Week 16)	2 weeks
Systemic corticosteroids > 10 mg prednisone equivalent** (until Week 16)	2 weeks
Intra-articular steroid injections (until Week 16)	4 weeks
Any biological immunomodulating agents, except those targeting TNFα*	No prior exposure
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)	No prior exposure
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)
Analgesics other than paracetamol/acetaminophen or low strength opioids PRN	4 weeks
Live vaccinations	6 weeks

* These agents fall under the category of biologic immunomodulators and are prohibited medications. Administration of these agents requires study treatment discontinuation (see Section 5.5.9).

** See details about corticosteroid management in Section 5.5.7

5.5.9 Discontinuation of study treatment and premature withdrawal

Patients may voluntarily discontinue from the study for any reason at any time. They may be considered discontinued if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature discontinuation occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature discontinuation from the study and record this information on the appropriate Study Phase Completion eCRF.

Patients who discontinue study should undergo an end of treatment visit (corresponding to the last visit for the patient's current period of treatment: e.g., Week 24, Week 52, Week 104, Week 208) at 4 weeks after last study treatment and then also return after an additional 8 weeks for a final follow-up visit, corresponding to Week F112 or Week F216, respectively (12 weeks after last study treatment; see Table 6-1 and Table 6-2). The final follow-up visit should be performed before any new treatment other than secukinumab is initiated. Study treatment discontinuation must also be recorded in IRT.

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

Patients who are prematurely discontinued from the study will not be replaced.

5.5.9.1 Discontinuation of study treatment

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

- Withdrawal of informed consent
- Emergence of the following adverse events:
  a. Any severe or serious adverse event that is not compatible with administration of study medication, including adverse events that require treatment with prohibited 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. Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the patient at a safety risk for continuation in the study (A general guidance on clinically notable laboratory values is provided in Appendix 1.)
  e. Pregnancy
  f. Use of any biologic immunomodulating agent except secukinumab (see Section 5.5.6 for washout periods)
  g. Any protocol deviation that results in a significant risk to the patient's safety

In addition to these requirements for study treatment discontinuation, the investigator should discontinue study treatment for a given patient if on balance, he/she thinks that continuation would be detrimental to the patient's well-being. For patients who were considered inadequate responders as outlined in Section 5.5.6, the investigator should consider discontinuing patients from study treatment who experience a clinically important worsening of disease activity compared to baseline at two consecutive visits after inadequate responder status was confirmed. A clinically important worsening will be defined as a worsening of BASDAI $\geq$ 20% AND $\geq$ 1

unit (0-10 scale), which represents the minimum clinically important difference (Pavy et al. 2005).

5.5.10 Withdrawal of consent

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

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

5.5.11 Loss to follow-up

For patients 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 trying to contact the patient and by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

5.5.12 Emergency breaking of assigned treatment code

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, investigational treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using

the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

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

Study medication must be discontinued after emergency unblinding.

In the case of accidental unblinding, patients will not be replaced by an equal number of newly enrolled patients.

5.5.13 Study completion and post-study treatment

A patient will be considered to have completed the core phase if he/she received a maximum of 100 weeks of study treatment and upon completion of the scheduled study assessments and procedures up to and including Visit F112 or continuation into the extension phase.

A patient will be considered to have completed the extension phase if he/she has received an additional 16 weeks of study treatment and has completed the scheduled study assessments and procedures up to and including Visit F216.

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

In any case, the investigator or site staff must contact the IRT as soon as possible to record the patient's study completion (Visit F112 for the core phase/Visit F216 for the extension phase) and/or discontinuation.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include initiating another treatment outside of the study as deemed appropriate by the investigator. 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.

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator

will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 and Table 6-2 list all of the assessments and indicates with an "x" when the visits are performed.

Patients should be seen for all visits on the designated day or as close to it as possible.

Patients who prematurely discontinue during a specific treatment period should return for the final visit within that treatment period (4 weeks after the last study treatment administration), as well as return for the follow-up visit 12 weeks after the last study treatment administration.

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.

Screening will be flexible in duration based on the time required to washout prior anti-rheumatic and other medications and will have a duration of up to 10 weeks, during which time the patient will sign the informed consent form (ICF), be evaluated for eligibility and sufficient time is allowed for potential medication washout, in addition to all other assessments indicated in Table 6-1.

Screening will consist of two consecutive visits. During Screening visit 1, initial assessments will be performed as outlined in Table 6-1. At that visit, the duration of the washout period will be determined and Screening visit 2 will be performed as follows:

- If the washout period is ≤ 4 weeks the investigator should proceed directly to Screening visit 2 on the same day and complete all assessments in the next 4 weeks prior to randomization.
- If the washout period is more than 4 weeks, the patient will be instructed to initiate the necessary washout regimen and return for Screening visit 2 at 4 weeks prior to randomization.

The rationale is that in all cases Screening visit 2 must occur within the 4 weeks prior to randomization.

All patients evaluated at Screening visits 1 and 2 for eligibility should not be screen failed on the basis of a medication requiring washout, unless the patient will be unable to complete the washout in the appropriate time frame before randomization

At a minimum, patients will be contacted for safety evaluations during the 30 days following the last study visit, however preferably for a follow up visit F112 for the core phase/Visit F216 for the extension phase, 12 weeks after last study treatment. Attempts to contact the patient should be recorded in the source documentation.

Table 6-1 Assessment schedule: Core phase

	Screening[1]		Treatment Period 1										Treatment Period 2							Treatment Period 3								Follow up
Week	**SV1 -10 to -4**	**SV2 ≤ -4**	**BSL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24***	**28**	**32**	**36**	**40**	**44**	**48**	**52***	**56 & 60**	**64**	**68 & 72**	**76**	**80 & 84**	**88**	**92, 96&100**	**104***	**F112***
Optional site visit																				X		X		X		X		
[redacted]																												
Inclusion/Exclusion criteria[2]	X	X	X																									
Relevant medical history/ current medical condition[2]	X	X	X																									
Prior medication	X	X	X																									
nr-axSpA assessment and history of extra-axial involvement[3]	X																											
Demography	X																											
MRI (spine and sacroiliac joints)	X[11]									X									X								X	
[redacted]																												
X-Ray of sacroiliac joints	X[4]																										X	
Cardiovascular medical history			X																									
Smoking history			X																									
Physical Exam		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S		S		S		S		S	S
Height		X																										

	Screening[1]		Treatment Period 1										Treatment Period 2							Treatment Period 3								Follow up
Week	**SV1 -10 to -4**	**SV2 |≤ -4**	**BSL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24***	**28**	**32**	**36**	**40**	**44**	**48**	**52***	**56 & 60**	**64**	**68 & 72**	**76**	**80 & 84**	**88**	**92, 96&100**	**104***	**F112***
Weight		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		X	X
PPD skin test[5] or QuantiFERON TB-Gold test		X																										
Chest X-ray or MRI[6]		S																										
Hematology, blood chemistry, urinalysis		X	X	X	X		X	X	X	X		X	X			X			X		X		X		X		X	X
Serum pregnancy test		X																										
Hepatitis B, C or HIV serology (only in countries where required)**		S																										
Urine pregnancy test			X				X			X		X				X			X		X		X		X		X	X
ECG			X							X									X								X	X
Randomization via IRT			X																									
[redacted]																												
Responder assessment via IRT											X	X	X	X	X	X	X	X										
On-site administration of s.c. study treatment by PFS[7]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[7]	X	X[7]	X	X[7]	X	X[7]			
Concomitant medication / non-drug therapy	X	Updated as necessary																										

	Screening[1]		Treatment Period 1										Treatment Period 2							Treatment Period 3								Follow up
Week	**SV1 -10 to -4**	**SV2 ≥ -4**	**BSL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24***	**28**	**32**	**36**	**40**	**44**	**48**	**52***	**56 & 60**	**64**	**68 & 72**	**76**	**80 & 84**	**88**	**92, 96&100**	**104***	**F112***
Adverse events/SAEs (including injection site reactions)[8]	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	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	X		X		X		X		X	X
BASFI			X	X	X	X	X	X	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	X		X		X		X		X	X
[redacted]																												
ASQoL			X					X		X		X							X				X				X	X
[redacted]																												
SF-36 v2			X					X		X		X							X				X				X	X
[redacted]																												

	Screening[1]		Treatment Period 1										Treatment Period 2							Treatment Period 3								Follow up
Week	**SV1 -10 to -4**	**SV2 |< -4**	**BSL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24***	**28**	**32**	**36**	**40**	**44**	**48**	**52***	**56 & 60**	**64**	**68 & 72**	**76**	**80 & 84**	**88**	**92, 96&100**	**104***	**F112***
[redacted]																												
High sensitivity C-Reactive protein (hsCRP)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X
HLA-B27		X																										
[redacted]																												
Lipids[9]			X					X		X									X								X	
[redacted]																												
Treatment period 1 completion form												X																
Treatment period 2 completion form																			X									
Treatment period 3 completion form																											X	

S Source data only

[1] If the patient'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 eCRF available at SV1

[3] Extra-axial involvement such as uveitis, psoriasis, inflammatory bowel disease, dactylitis, enthesitis, peripheral arthritis

[4] Unless X-ray according to the imaging criteria was taken within the past 3 months prior Screening

[5] 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.

[6] 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 patient meets inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation. The X-ray may be replaced by an MRI assessment.

[7] After Week 52, patients able to self-administer can do so at home and don't have to attend the site at these specified visits

[8] AEs/SAEs occurring after the patient has signed the informed consent must be captured on the appropriate eCRF page.

[9] Sample must be obtained fasting.

[redacted]

[11]Unless MRI according to the imaging criteria was taken within the past 3 months prior to targeted Baseline

* For all patients who discontinue the study prematurely, the investigator should ensure that the patient completes an end of treatment visit (corresponds to the last visit for the patient's current treatment period) 4 weeks after last study treatment to complete assessments shown for Week 104, and also returns after an additional 8 weeks for a final follow-up visit, F112 (12 weeks after last study treatment). The final visit should be performed before any new treatment other than secukinumab is initiated.
All patients that continue into the extension phase will have their first extension phase visit at the last treatment period visit of the core phase (week 104) and will skip the follow-up visit F112.

** 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

Table 6-2 Assessment schedule: Extension phase

Period /Visit name	16-week dose escalation treatment period					Continuous treatment period[14]											EoT *	Follow up*
Week	104[12]	108	112	116	120	124/128/132	136	140/144/148	152	156/160/164	168	172/176/180	184	188/192/196	200	204	208	216
Optional site visit		X		X		X		X		X		X		X		X		
Obtain informed consent[13]	X																	
Inclusion/Exclusion criteria	X																	
Physical Exam			X		X		X		X		X		X		X		X	X
Weight																	X	
Vital signs			X		X		X		X		X		X		X		X	X
Randomization in IRT	X																	
Patient's global assessment of disease activity (VAS)			X		X				X				X				X	
Patient's assessment of back pain intensity (VAS)			X		X				X				X				X	
BASFI			X		X				X				X				X	
BASDAI			X		X				X				X				X	
[redacted]																		
ASQoL			X		X				X				X				X	
SF-36			X		X				X				X				X	
[redacted]																		

Period /Visit name	16-week dose escalation treatment period					Continuous treatment period[14]											EoT *	Follow up*
Week	104[12]	108	112	116	120	124/128/132	136	140/144/148	152	156/160/164	168	172/176/180	184	188/192/196	200	204	208	216
High sensitivity C-Reactive Protein (hsCRP)			X		X		X		X		X		X		X		X	
Hematology, blood chemistry, urinalysis			X		X		X		X		X		X		X		X	X
Serum pregnancy test																	X	X
Urine pregnancy test			X		X		X		X		X		X		X			
[redacted]																		
On-site administration of s.c. study treatment by PFS[15]	X	X[15]	X	X[15]	X	X[15]	X	X[15]	X	X[15]	X	X[15]	X	X[15]	X	X[15]		
Concomitant medication / non-drug therapy	X	Update as necessary																
Adverse events/SAEs (including injection site reactions)[8]	X	Update as necessary																

[8] AEs/SAEs occurring after the patient has signed the informed consent must be captured on the appropriate eCRF page.

[12] The Week 104 visit of the core phase will be the first visit in the extension phase

[13] Patients have to sign a new ICF for participation in the extension phase

[14] Depending on the timing for each patient, some of these visits might not be conducted and the patient will go directly to the EoT (End of Treatment) visit

[15] Patients able to self-administer can do so at home and don't have to come to the site at these specified visits

* For all patients who discontinue the study prematurely, the investigator should ensure that the patient completes an end of treatment visit Week 208, 4 weeks after last study treatment to complete assessments shown for Week 208, and also returns after an additional 8 weeks for a final follow-up visit, F216 (12 weeks after last study treatment). The final visit should be performed before any new treatment other than secukinumab is initiated.

6.1 Information to be collected on screening failures

Patients may discontinue from the study prior to randomization. These patients are considered screening failures.

If a patient discontinues before entering the double-blind treatment period at baseline, IRT must be notified within 2 days and the reason for not being randomized will be entered on the Screening Phase Disposition eCRF page. In addition, only the following eCRFs should be completed: Demography eCRF, Informed Consent eCRF, Inclusion/Exclusion eCRF, and the Adverse event (AE) eCRF 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.

All patients who have signed informed consent and are randomized into the Treatment period 1 of the study will have all adverse events **occurring after informed consent is signed** recorded on the Adverse Event eCRF and as SAE if applicable, i.e. when SAE criteria are met.

Investigators will have the discretion to record abnormal test findings on the medical history eCRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.2 Patient demographics/other baseline characteristics

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

- Date of birth, age, sex, race, ethnicity and source of patient referral
- Relevant nr-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), date of onset of inflammatory back pain, number of previous DMARDs used, date of diagnosis of nr-axSpA, previous nr-axSpA therapies, cardiovascular medical history and smoking history

Whenever possible, diagnoses and not symptoms will be recorded here.

6.3 Treatment exposure and compliance

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

Drugs administered prior to start of treatment and other drugs continuing or started during the study treatment period will be entered in the Prior/Concomitant medications or Significant non-drug therapies eCRF page.

Compliance is expected to be 100%, unless temporary interruption is needed for safety reasons as described in Section 5.5.5. Compliance will also be assessed by a Novartis/CRO monitor using information provided by the authorized site personnel.

6.4 Efficacy

- Assessment of SpondyloArthritis International Society criteria (ASAS)

- Patient's global assessment of disease activity (VAS)
- Patient's assessment of back pain intensity (VAS)
- Bath Ankylosing Spondylitis Functional Index (BASFI)
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- [redacted]
- hsCRP [redacted]
- [redacted], ASDAS-CRP [redacted] response categories
- [redacted]
- MRI of spine and sacroiliac joints
- [redacted]
- X-ray of the sacroiliac joints

6.4.1 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:

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

6.4.1.1 ASAS Response Criteria-20% (ASAS20)

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

6.4.1.2 ASAS Response Criteria-40% (ASAS 40)

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

6.4.1.3 ASAS 5/6 improvement criteria

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

6.4.1.4 ASAS partial remission criteria

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

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

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

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

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

6.4.4 Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those patients with AS. The ten questions were chosen with major input from patients with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the patients' ability to cope with everyday life. A 0 through 10 scale (captured by 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.

6.4.5 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

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

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

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

6.4.5.1 BASDAI 50

The BASDAI 50 is defined as an improvement of at least 50% in the BASDAI compared to baseline.

[redacted]

6.4.8 High sensitivity C-reactive protein (hsCRP)

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

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

[redacted]

6.4.10 [redacted] ASDAS-CRP [redacted] response categories

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

The [redacted] ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score) will be utilized to assess the disease activity status. Parameters used for the ASDAS include spinal 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 [redacted] (Sieper et al 2009, Lukas et al 2009).

Disease activity states are inactive disease, moderate disease activity, high disease activity, and very high disease activity. The 3 values selected to separate these states were < 1.3 between inactive disease and 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 were a change ≥ 1.1 unit for "minimal clinically important improvement" and a change ≥ 2.0 units for "major improvement" (Machado et al 2011).

[redacted]

6.4.12 MRI

MRIs will be obtained as defined in the schedule of assessments (Table 6-1) and according to the imaging acquisition guidelines provided by the central imaging lab. The MRI for each

patient will include T1 and STIR sequences of the sagittal spine (cervical, thoracic and lumbar) and oblique coronal of the pelvis including both sacroiliac joints. These MRI images should be transferred as anonymized electronic files to the central imaging lab following acquisition. The central imaging lab will conduct independent review for all spine and sacroiliac MR imaging in this trial.

6.4.13 X-ray

X-rays will be obtained as defined in the schedule of assessments (Table 6-1) and according to the imaging acquisition guidelines provided by the central imaging lab. The X-ray requirements include [redacted] anterio-posterior view of the pelvis including visibility of both sacroiliac joints for modified New York AS determination. These images should be transferred to the central imaging lab following acquisition. Some X-rays may need to be repeated if deemed unevaluable by central review. In case of insufficient quality, the center will be advised and trained on any quality issues prior to the repeat X-ray, to keep any repeat X-rays to a minimum.

The central imaging lab will conduct independent review for all spine and sacroiliac X-rays in this trial.

6.4.14 Appropriateness of efficacy assessments

The efficacy outcome measures used in this study are the standard measures used across all AS and nr-axSpA trials and are considered to be required for filing.

This study involves exposure to radiation from a possible chest X-ray, as well as X-rays of part of the thoracic, the cervical and lumbar spine and the SIJs. The radiation exposure from these procedures is not necessary for medical care but is intended for research purposes only.

The amount of cumulative *annual* radiation in this study is about 3.4 mSv for the combined X-ray procedures and is based on effective doses for various diagnostic radiological procedures reported in literature (Mettler et al 2008). This exposure is comparable to the natural radiation an average person receives in one year. The radiation dose between 3 mSv and 50 mSv is considered ‘minimal’ (Stabin et al 2009). Therefore, the radiation exposure in this study involves minimal risk and is necessary to obtain the research information desired.

6.5 Safety

- QuantiFERON TB-Gold test or PPD skin test
- Chest X-ray or MRI
- Physical examination
- Vital signs
- Height and weight
- Laboratory evaluations
- [redacted]
- Electrocardiogram
- Pregnancy and assessment of fertility

- Local tolerability (Injection site reactions)
- Tolerability of secukinumab

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.

6.5.1 QuantiFERON TB-Gold test or PPD skin test

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

QuantiFERON TB-Gold test

A QuantiFERON TB-Gold test is to be performed at the second screening visit and the results to be available prior to randomization to determine the patient's eligibility. The test will be used to screen the patient 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.

PPD skin test

A PPD skin test is to be performed at screening and read before randomization to determine the patient's eligibility for the trial. 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.

Since the reaction (induration) will take 48-72 hours to develop, the patients must return to the investigators' site within that time for a proper evaluation of the injection site. This will determine whether the patient 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.

6.5.2 Chest X-ray or MRI

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, tuberculosis.

6.5.3 Physical examination

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

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

6.5.4 Vital signs

This 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.

6.5.5 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing) (both 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.

6.5.6 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected 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 Appendix 1. All patients with laboratory tests containing clinically significant abnormal values are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

6.5.6.1 Hematology

Hemoglobin, platelet, red blood cell, white blood cell (WBC) and differential white blood cell counts will be measured at scheduled visits.

6.5.6.2 Clinical 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.

6.5.6.3 Lipid panel

A lipid profile including High Density Lipoprotein, Low Density Lipoprotein, cholesterol and triglycerides will be measured from a fasting blood sample.

A cardiovascular profile including lipoprotein (a), apolipoprotein B, apolipoprotein A-1, and adiponectin will be measured from a fasting blood sample.

6.5.6.4 Urinalysis

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

6.5.8 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as indicated in Table 6-1.

All ECGs must be performed on the ECG machines provided for the study.

All ECGs will be independently reviewed. Instructions for the collection and transmission of the ECGs to the independent reviewer will be provided in the ECG investigator manual.

Clinically relevant abnormalities should be recorded on the relevant medical history/Current medical conditions eCRF page for the baseline ECG.

Clinically relevant abnormalities noted after the baseline ECG should be reported as AE (Section 7.1).

6.5.9 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum β-hCG test (serum pregnancy test) performed at the second screening visit and local urine pregnancy tests as indicated in Table 6-1 and Table 6-2. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative.

6.5.10 Local tolerability (Injection site reactions)

The local tolerability at the site of s.c. injection of the study treatment will be assessed in case of any local reaction, until this has disappeared**.**

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

6.5.11 Tolerability of secukinumab

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

6.5.12 Appropriateness of safety measurements

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

The safety measures used in this study are reliable and relevant standard measures for a biologic in nr-axSpA.

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

6.6 Other assessments

- Health-related Quality of Life
- [redacted]
- HLA-B27
- [redacted]
- [redacted]
- [redacted]

6.6.1 Health-related Quality of Life and Patient Reported Outcome

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

- SF-36
- ASQoL
- [redacted]
- [redacted]
- [redacted]

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

All questionnaires will be completed at the scheduled study visit prior to the patient seeing the investigator for any other clinical assessment or evaluation. The patient should be given sufficient instruction, space, time and privacy to complete the questionnaires. The study coordinator should check each questionnaire for completeness and encourage the patient to complete any missing responses. Guidelines for administering the PRO questionnaires can be

found in Appendix 8. 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 for any unsolicited comments written by the patient. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Appendix 8 of the protocol. Investigators should not encourage the patients 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.

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

The SF-36 is a widely used and extensively studied instrument to measure health-related 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 and the Mental Component Summary also can be computed (McHorney et al 1993). The SF-36 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual patients.

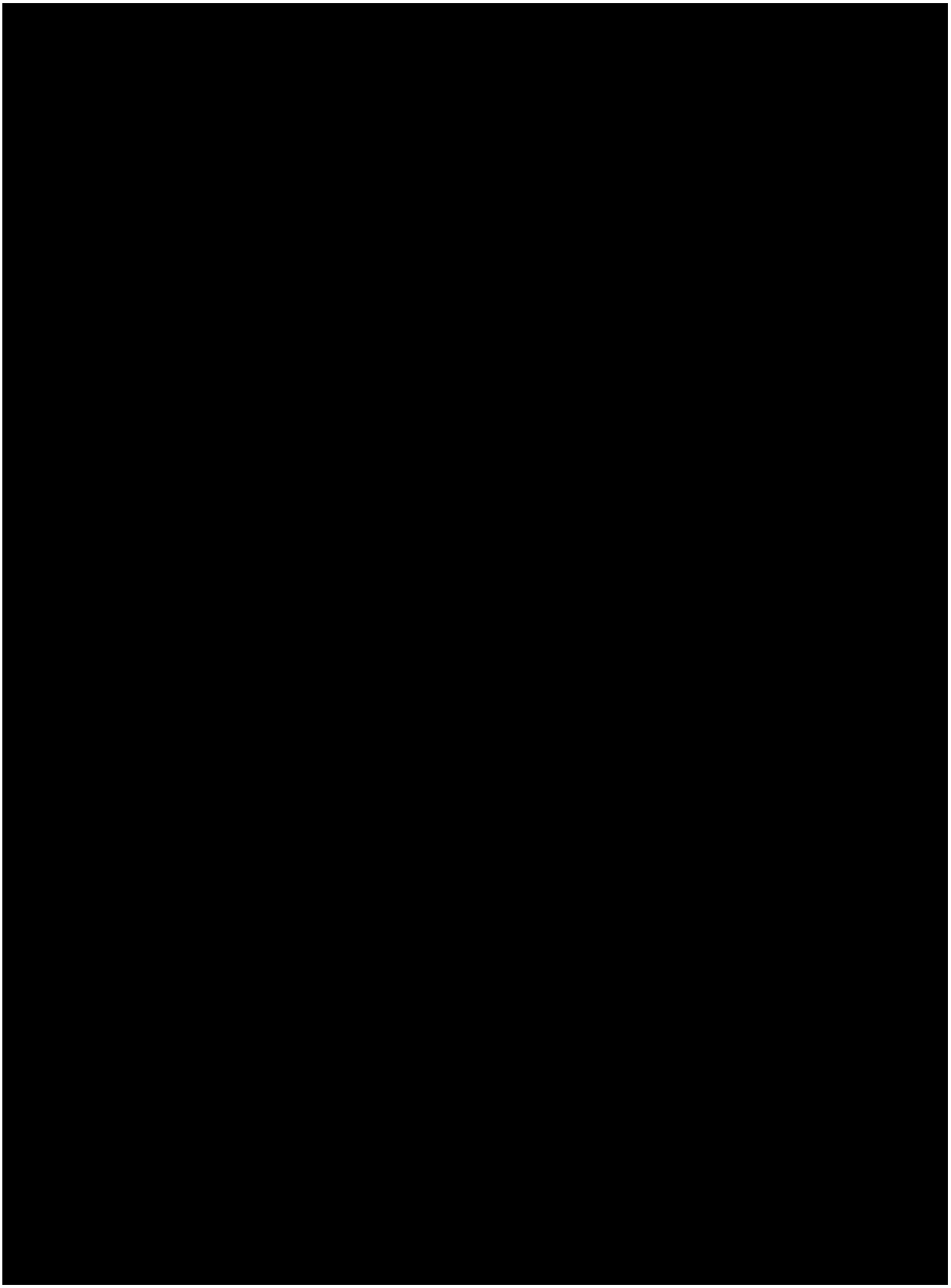
The purpose of the SF-36 in this study is to assess the health-related QoL of patients. Given the acute nature of this disease, version 2, with a 1-week recall period, will be used in this study.

The use of the SF-36, especially the SF-36 physical component summary (PCS), in patients with nr-axSpA can be supported. While SF-36 was widely used to assess the health related quality of life in AS patients, a recent study investigated the questionnaire in both, AS and nr-axSpA patients, within one trial. Specifically for the SF-36 PCS which will be included as a secondary objective in this trial, van Tubergen et al. 2015 found good test-retest reliability, good construct and known-groups validity as well as good correlations with clinical outcomes in nr-axSpA.

6.6.1.2 Ankylosing Spondylitis Quality of Life (ASQoL)

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

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



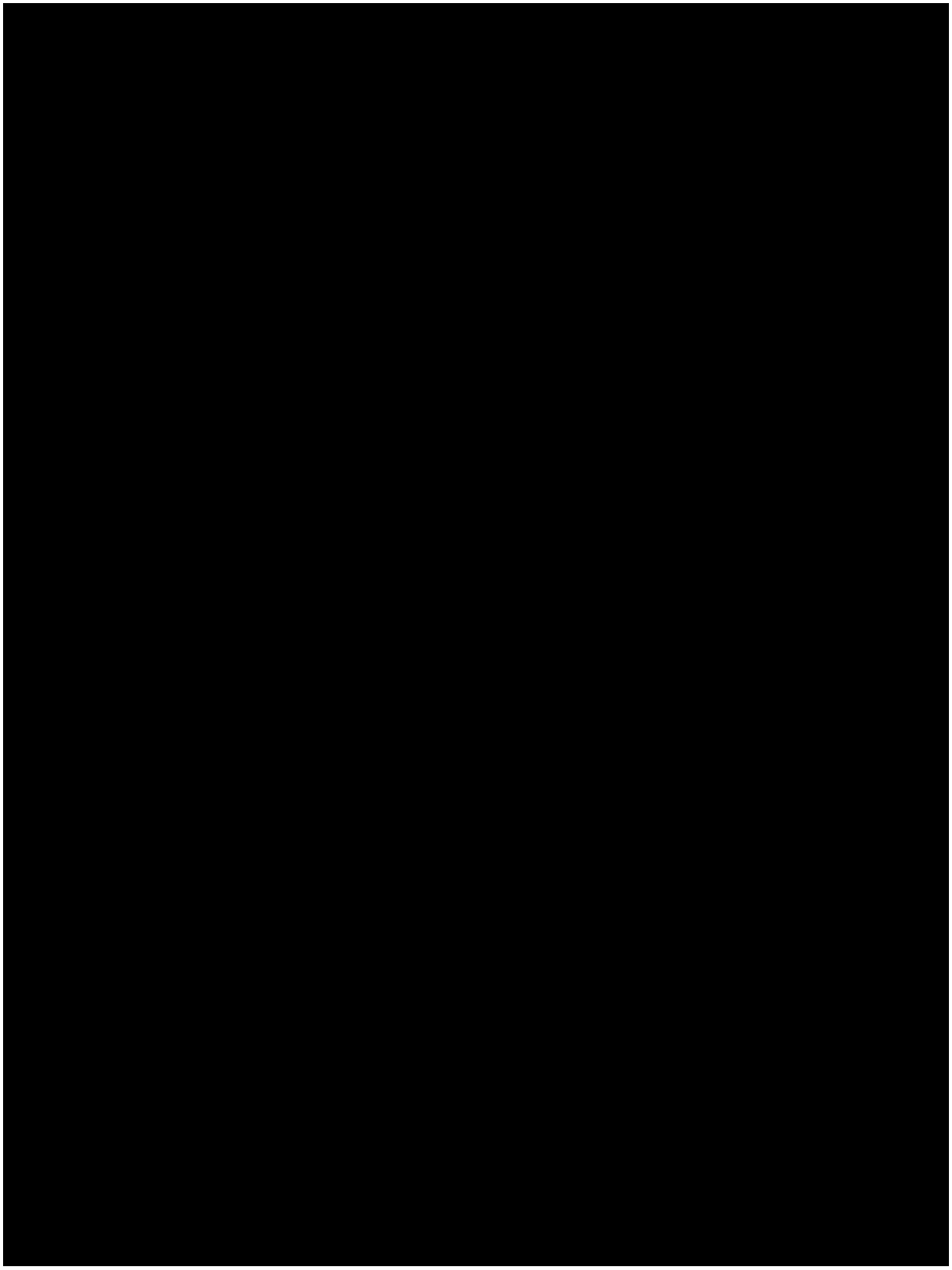
[redacted]

6.6.3 HLA-B27

A blood sample to analyze Human Leukocyte Antigen-B27 (HLA-B27) will be obtained from all patients at screening.

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

[redacted]



7 Safety monitoring

7.1 Adverse events

An AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient 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 occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

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 should 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 patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included in Appendix 1.

Adverse events should be recorded in the AE eCRF under the signs, symptoms, or diagnosis associated with them, accompanied by the following information.

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment (no/yes)
- its duration (start and end dates), or if the event is ongoing, an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE)
- action taken regarding study treatment
- whether other medication or therapies have been taken (concomitant medication/non- drug therapy)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

Information about common side effects already known about the investigational drug can be found in the IB or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

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:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

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

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

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

All AEs (serious and non-serious) are captured on the eCRF, SAEs also require individual reporting to Drug Safety and Epidemiology (DS&E) as per Section 7.2.2.

7.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 12 weeks after last administered dose of study treatment must be reported to Novartis/CRO within 24 hours of learning of its occurrence.

Any SAEs experienced after this period should only be reported to Novartis/CRO if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow-up information) is collected and recorded in English on the paper Serious Adverse Event Report Form or the electronic Serious Adverse Event Form within the EDC system (where available). The Investigator must assess the relationship to each specific component of the study treatment (if the study treatment consists of several components).

SAEs (initial and follow-up) that are recorded *on the paper SAE form* should be faxed within 24 hours of awareness of the SAE to the local Novartis/CRO Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of DS&E, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

SAEs (initial and follow-up) that are recorded *electronically* in the EDC system should be submitted within 24 hours of awareness of the SAE or changes to an existing SAE. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis/CRO may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational 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 Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

There has been no safety signal for liver toxicity with secukinumab to date in over 9600 patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the liver. Standard liver function tests will be obtained at regular intervals, but special measures for liver safety monitoring are not planned. For further information on standard liver function tests, see Appendix 1.

7.4 Renal safety monitoring

There has been no safety signal for nephrotoxicity with secukinumab to date in over 9600 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 patients with laboratory tests containing clinically significant abnormal values (see Appendix 1 for notable laboratory values) are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined. Standard renal function tests (blood urea nitrogen, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

7.5 Pregnancy reporting

All pre-menopausal women who are not surgically sterile will have a urine pregnancy test. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative.

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis/CRO within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The study drug must be discontinued, though the patient may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments.

Pregnancy must be recorded on a Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis/CRO Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis/CRO study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8 Data review and database management

The study originally used two data collection systems, eSource and OC/RDC. The systems were chosen according to the countries and only one system was in place in each site. Due to the discontinuation of the eSource system, all sites using eSource will switch to OC/RDC and this will be the only data capture system in the study moving forward. All collected data from eSource will be provided to the sites for documentation and will be included in OC/RDC.

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture tools 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 patient records, the accuracy of entries on the eCRFs, 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. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source records. 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. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

This study originally incorporated technology (eSource) to capture source documents and source data electronically, consistent with FDA guidance (CDER 2013) regarding electronic source and regulations related to the maintenance of adequate patient case histories (21CFR 312.62 (b)), but this was discontinued during the conduct of the study.

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis/CRO staff review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or

additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

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

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis /CRO.

ECG readings will be processed centrally and the results will be sent electronically to Novartis/CRO.

Randomization codes and data about all study drug(s) dispensed to the patient will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis /CRO.

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

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

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

An independent adjudication committee may be used to monitor specific safety events, including, but potentially not limited to clinically significant cardio- and cerebrovascular events. The events will be blindly reviewed and adjudicated as they occur during the conduct of the trial as applicable.

Details regarding the adjudication process will be available in the relevant secukinumab Adjudication Committee charter.

9 Data analysis

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

Data analyses will be presented by treatment group. Efficacy and safety data for Treatment Period 1 and Treatment Period 2 will be presented by the following three treatment groups. Patients may be included in more than one treatment group for some analyses (e.g., exposure-adjusted adverse events over the entire treatment period).

- Secukinumab 150 mg with loading regimen
- Secukinumab 150 mg with no loading regimen
- Placebo

Note that the treatment groups above for a patient may differ depending on the time period of the analysis and whether one assesses the patient for efficacy or safety (see Section 9.1 for details). Data may be presented by a combination of the 'original' and 'switch' treatment groups. These treatment groups represent the treatment combinations the patients experience over the course of the entire trial (e.g., placebo patients who are reassigned to 150 mg secukinumab).

9.1 Analysis sets

The following analysis sets will be used in this trial:

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

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

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

9.2 Patient 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 inflammatory back pain and nr-

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) and BASMI components (all seven in original units), presence of SIJ inflammation by MRI and each randomization strata level (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+).

Medical history

A history of nr-axSpA with focus on previous extra-articular involvement and past therapies for nr-axSpA will be obtained and summarized by treatment group. 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 patients with pre-solicited cardiovascular risk factors will be summarized by treatment group. The number of cardiovascular risk factors that each patient has will also be summarized by treatment group. If it is unknown whether or not a patient currently or previously experienced a specific cardiovascular risk factor, it will be assumed that cardiovascular risk factor did not occur for that patient.

9.3 Treatments

Study treatment

The analysis of study treatment data will be based on the safety set. The number of visits with active and placebo injections 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 patients with cumulative exposure levels (e.g., any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 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 study treatment and within 84 days after last dose 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 patients 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.

The number and percentage of patients receiving prior and concomitant nr-axSpA therapy will be presented by treatment group as well as the reasons for stopping their therapies (primary lack of efficacy, secondary lack of efficacy, lack of tolerability, other) and the total duration of

exposure to nr-axSpA therapies previously. [redacted] use will be summarized.

9.4 Analysis of the primary variable(s)

Details of the testing strategy including primary and secondary endpoints are provided in Section 9.5.

9.4.1 Variable(s)

Primary endpoint for analysis plan A

The primary efficacy variable is response to treatment according to the ASAS40 criteria at Week 16 in TNF naïve patients. The analysis of the primary variable will be based on the FAS patients.

Primary endpoint for analysis plan B

The primary efficacy variable is response to treatment according to the ASAS40 criteria at Week 52 in TNF naïve patients. The analysis of the primary variable will be based on the FAS patients.

9.4.2 Statistical model, hypothesis, and method of analysis

Primary endpoint for analysis plan A

The statistical hypothesis for ASAS40 being tested is that there is no difference in the proportion of TNF naïve patients fulfilling the ASAS40 criteria at Week 16 in secukinumab with loading regimen versus placebo regimen.

Let p_j denote the proportion of ASAS40 responders at Week 16 in TNF naïve patients for treatment regimens j, j=0, 1, where

- 0 corresponds to placebo regimen,
- 1 corresponds to secukinumab 150 mg with loading regimen,

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

H_1: secukinumab 150 mg with load is not different to placebo regimen with respect to ASAS40 response in TNF naïve patients at Week 16

The primary analysis will be conducted via logistic regression with treatment and stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) as factors and weight as a covariate. Odds ratios and 95% CI will be presented comparing secukinumab regimen to placebo.

Primary endpoint for analysis plan B

The statistical hypothesis for ASAS40 being tested is that there is no difference in the proportion of TNF naïve patients fulfilling the ASAS40 criteria (and did not escape) at Week 52 in secukinumab without loading regimen versus placebo regimen.

Let p_j denote the proportion of ASAS40 responders at Week 52 in TNF naïve patients for treatment regimens j, j=0, 1, where

- 0 corresponds to placebo regimen,

- 1 corresponds to secukinumab 150 mg without loading regimen,

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

H_1: secukinumab 150 mg without load is not different to placebo regimen with respect to ASAS40 response in TNF naïve patients at Week 52

The primary analysis will be conducted via logistic regression with treatment and stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) as factors and weight as a covariate. Odds ratios and 95% CI will be presented comparing secukinumab regimen to placebo.

9.4.3 Handling of missing values/censoring/discontinuations

Missing data for ASAS20/40 response and other binary efficacy variables (e.g., ASAS5/6, etc.) for data up to Week 52 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 52
2. Patients who do not have the required data to compute responses (e.g., ASAS components) at baseline and at the specific time point will be classified as non-responders at the specific time point.

Patients who are unblinded will be considered non-responders from the time of unblinding up to Week 52. The primary analysis will use non-responder imputation.

Continuous variables (e.g., ASAS components) with the exception of MRI endpoints, 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.

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

Data post treatment switch decision (see Section 5.5.6)

In general, data for patients where a decision was made to switch treatment will be handled in the following fashion up to Week 52:

- For binary endpoints, patients will be considered non-responders after switching. This will be done for all treatment regimens in order to minimize bias for between-treatment comparisons. However, the actual response rates will also be summarized without considering the patients as non-responders as they provide insight into the long-term response profile within each treatment regimen.
- For continuous endpoints (ASQoL and SI joint edema score on MRI), a composite estimand strategy will be applied and data after switch will be set to the worst possible outcome. Rank-based analysis will be used for hypothesis testing.
- If applicable, difference in trimmed means estimate will be used to summarize the treatment effect estimate for the continuous composite endpoint

- For continuous endpoints the actual observed values after switch will be also summarized with descriptive statistics
- A supplementary estimand principal stratum strategy might be used to quantify treatment effect in population of subjects who would adhere in case randomized to secukinumab
  -

9.4.4 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.

In order to determine the robustness of the logistic regression model used for the primary analysis, ASAS40 response in TNF naïve patients at Week 16 and Week 52 will also be evaluated using a non-parametric regression (Koch et al 1998) model with the same independent variables as the logistic regression model.

The impact of missing data on the analysis results of ASAS40 in TNF naïve patients 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 based on randomized treatment (based on patients providing data at a specific visit regardless of current treatment, i.e. also using data collected after switch decision point).
- Tipping point analysis

9.5 Analysis of secondary variables

9.5.1 Secondary efficacy variables

Secondary endpoints for analysis plan A

The secondary efficacy variables and the method for adjusting for multiplicity are described below. Secondary efficacy variables will be analyzed using the FAS population.

ASAS40 at Week 16

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

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 (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-α status as factors and weight as a covariate.

BASDAI at Week 16

Between-treatment differences in the change from baseline in BASDAI will be evaluated using MMRM with treatment group, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+), TNF-α status, 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. The significance of the treatment effect for secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

BASDAI50 at Week 16

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

hsCRP at Week 16

For the change in hsCRP, since evidence from the literature would suggest that the data are not normally distributed (Huffman et al 2006), analysis will be performed on the $\log_e$ ratio of the treatment value vs baseline value (calculated by dividing the post-baseline value by the baseline value and then applying the $\log_e$ transformation) to normalize the distribution of hsCRP at each analysis visit. Between-treatment differences in the change in hsCRP relative to baseline will be evaluated using MMRM with treatment group, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+), TNF-α status, 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 significance of the secukinumab treatment effect for secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits. The estimate and the 2-sided 95% confidence intervals obtained from the model will be back transformed to the original scale.

SF-36 PCS at Week 16

See Section 9.5.4.

ASQoL at Week 16

See Section 9.5.4.

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 (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-α status 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 (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+), TNF-α status, 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. The significance of the treatment effect for secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

SI joint edema on MRI at Week 16

The change from baseline to Week 16 in inflammation measured by SI joint total edema score will be evaluated using an analysis of covariance (ANCOVA) model with treatment group, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-α status as factors, and weight and baseline inflammation score as covariates.

Supportive analysis for SI joint edema on MRI will be performed as follows:

- Using a non-parametric ANCOVA model on multiple imputation data
- Using an ANCOVA model where instead of multiple imputation missing data is handled by Baseline observation carried forward (BOCF)

ASAS partial remission at Week 16

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

Testing strategy for analysis plan A

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 150 mg (with load) is not different to placebo regimen with respect to ASAS40 response in TNF naïve patients at Week 16

Secondary objectives:

H_2: secukinumab 150 mg (with load) is not different to placebo regimen with respect to ASAS40 response at Week 16

H_3: secukinumab 150 mg (with load) is not different to placebo regimen with respect to ASAS 5/6 response at Week 16

H_4: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from baseline in total BASDAI at Week 16

H_5: secukinumab 150 mg (with load) is not different to placebo regimen with respect to BASDAI50 at Week 16

H_6: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from baseline in hsCRP at Week 16

H_7: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from baseline in BASFI at Week 16

H_8: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from screening in SI joint edema on MRI at Week 16

H_9: secukinumab 150 mg (with load) is not different to placebo regimen with respect to ASAS20 at Week 16

H_{10}: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from baseline in SF-36 PCS at Week 16

H_{11}: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from baseline in ASQoL at Week 16

H_{12}: secukinumab 150 mg (with load) is not different to placebo regimen with respect to ASAS partial remission at Week 16

H_{13}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to ASAS40 response in TNF naïve patients at Week 16

H_{14}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to ASAS40 response at Week 16

H_{15}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to ASAS 5/6 response at Week 16

H_{16}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to change from baseline in total BASDAI at Week 16

H_{17}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to BASDAI50 at Week 16

H_{18}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to change from baseline in hsCRP at Week 16

H_{19}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to change from baseline in BASFI at Week 16

H_{20}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to change from screening in SI joint edema on MRI at Week 16

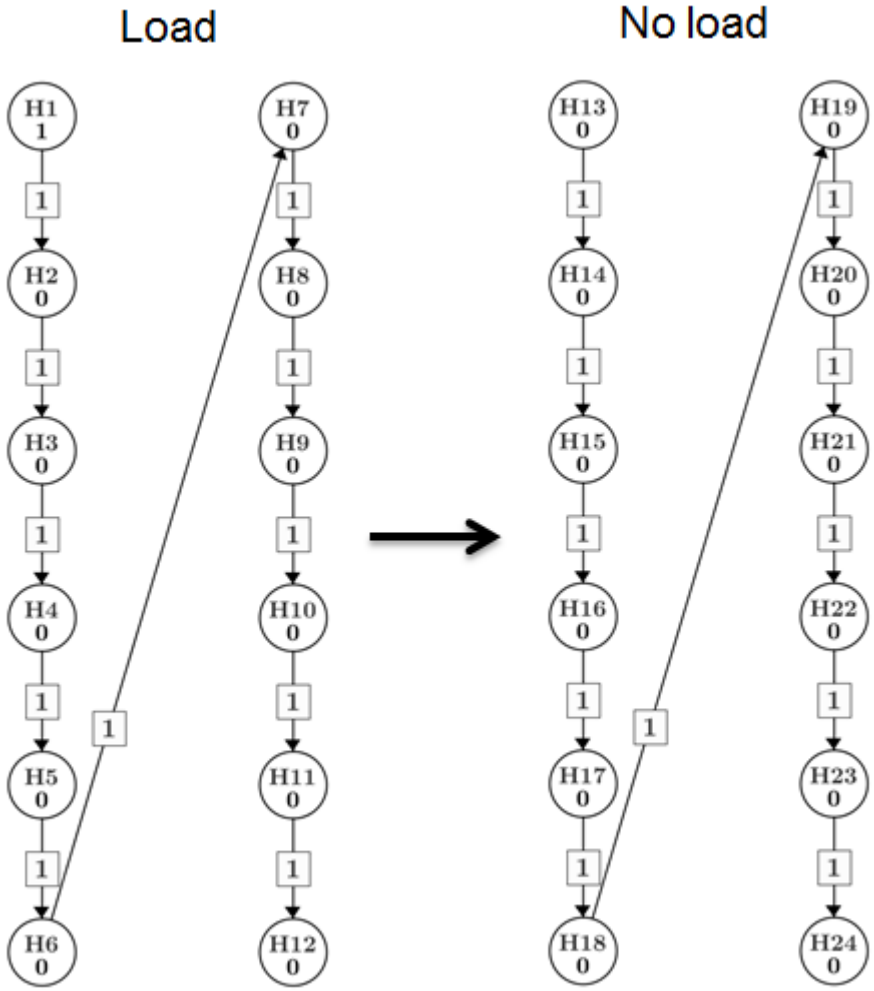
H_{21}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to ASAS20 at Week 16

H_{22}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to change from baseline in SF-36 PCS at Week 16

H_{23}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to change from baseline in ASQoL at Week 16

H_{24}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to ASAS partial remission at Week 16

Figure 9-1 Testing strategy for analysis plan A



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 9-1. The primary hypothesis (H_1) for the primary objective (ASAS40 in TNF naïve at Week 16) for secukinumab with load 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. If H_{12} is rejected then the full α-level is passed on to the testing sequence of secukinumab without load which can now be tested at 5% level sequentially in a similar way.

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.

Secondary endpoints for analysis plan B

The secondary efficacy variables and the method for adjusting for multiplicity are described below. Secondary efficacy variables will be analyzed using the FAS population.

ASAS40 at Week 52

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

ASAS40 at Week 16

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

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 (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-α status as factors and weight as a covariate.

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 (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-α status as factors and weight as a covariate.

BASDAI at Week 16

Between-treatment differences in the change from baseline in BASDAI will be evaluated using MMRM with treatment group, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+), TNF-α status, 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. The significance of the treatment effect for secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

SF-36 PCS at Week 16

See Section 9.5.4.

ASQoL at Week 16

See Section 9.5.4.

ASQoL at Week 52

The change from baseline to Week 52 in ASQoL score will be analyzed by composite estimand strategy in which data after switch is set to worst possible value. Wilcoxon rank-sum test will be used for testing the difference in distributions of the composite endpoint in active vs placebo. If observed switching rate allows, treatment differences will be summarised using trimmed means and confidence intervals will be calculated using bootstrap.

Total direct effect (principal stratum) estimand may be presented as supplementary estimand for treatment effect in population adhering to treatment in case of randomized to secukinumab.

SI joint edema on MRI at Week 16

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

Supportive analysis for SI joint edema on MRI will be performed as follows:

- Using a non-parametric ANCOVA model on multiple imputation data
- Using an ANCOVA model where instead of multiple imputation missing data is handled by BOCF

SI joint edema on MRI at Week 52

The change from baseline to Week 52 in inflammation measured by SI joint total edema score will be analyzed by composite estimand strategy in which data after switch is set to worst possible value. Wilcoxon rank-sum test will be used for testing the difference in distributions of the composite endpoint in active vs placebo. If observed switching rate allows, treatment differences will be summarized using trimmed means and confidence intervals will be calculated using bootstrap.

Total direct effect (principal stratum) estimand may be presented as supplementary estimand for treatment effect in population adhering to treatment in case of randomized to secukinumab.

hsCRP at Week 16

For the change in hsCRP, since evidence from the literature would suggest that the data are not normally distributed (Huffman et al 2006), analysis will be performed on the $\log_e$ ratio of the treatment value vs baseline value (calculated by dividing the post-baseline value by the baseline value and then applying the $\log_e$ transformation) to normalize the distribution of hsCRP at each analysis visit. Between-treatment differences in the change in hsCRP relative to baseline will be evaluated using MMRM with treatment group, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+), TNF-α status, 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 significance of the secukinumab treatment effect for secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits. The estimate and the 2-sided 95% confidence intervals obtained from the model will be back transformed to the original scale.

BASFI at Week 16

Between-treatment differences in the change from baseline in BASFI will be evaluated using MMRM with treatment group, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+), TNF-α status, 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. The significance of the treatment effect for secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

BASDAI50 at Week 16 and Week 52

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

ASDAS-CRP inactive disease at Week 52

Response at Week 52 to ASAS partial remission will be evaluated using a logistic regression model with treatment, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and TNF-α status as factors and baseline weight and ASDAS-CRP score as covariates.

Testing strategy for analysis plan B

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 150 mg (without load) is not different to placebo regimen with respect to ASAS40 in TNF naïve at Week 52

Secondary objectives:

H_2: secukinumab 150 mg (without load) is not different to placebo regimen with respect to ASAS40 at Week 52

H_3: secukinumab 150 mg (without load) is not different to placebo regimen with respect to ASAS40 at Week 16

H_4: secukinumab 150 mg (with load) is not different to placebo regimen with respect to ASAS40 in TNF naïve at Week 52

H_5: secukinumab 150 mg (with load) is not different to placebo regimen with respect to ASAS40 at Week 52

H_6: secukinumab 150 mg (with load) is not different to placebo regimen with respect to ASAS40 at Week 16

H_7: secukinumab 150 mg (without load) is not different to placebo regimen with respect to change from baseline in total BASDAI at Week 16

H_8: secukinumab 150 mg (without load) is not different to placebo regimen with respect to BASDAI50 at Week 16

H_9: secukinumab 150 mg (without load) is not different to placebo regimen with respect to BASDAI50 at Week 52

H_{10}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to change from baseline in hsCRP at Week 16

H_{11}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to change from baseline in SF-36 PCS at Week 16

H_{12}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to change from baseline in ASQoL at Week 16

H_{13}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to ASAS5/6 at Week 16

H_{14}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to ASAS20 at Week 16

H_{15}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to change from baseline in BASFI at Week 16

H_{16}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to change from screening in SI joint edema on MRI at Week 16

H_{17}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to ASDAS-CRP ID at Week 52

H_{18}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to change from baseline in ASQoL at Week 52

H_{19}: secukinumab 150 mg (without load) is not different to placebo regimen with respect to change from screening in SI joint edema on MRI at Week 52

H_{20}: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from baseline in total BASDAI at Week 16

H_{21}: secukinumab 150 mg (with load) is not different to placebo regimen with respect to BASDAI50 at Week 16

H_{22}: secukinumab 150 mg (with load) is not different to placebo regimen with respect to BASDAI50 at Week 52

H_{23}: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from baseline in hsCRP at Week 16

H_{24}: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from baseline in SF-36 PCS at Week 16

H_{25}: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from baseline in ASQoL at Week 16

H_{26}: secukinumab 150 mg (with load) is not different to placebo regimen with respect to ASAS5/6 at Week 16

H_{27}: secukinumab 150 mg (with load) is not different to placebo regimen with respect to ASAS20 at Week 16

H_{28}: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from baseline in BASFI at Week 16

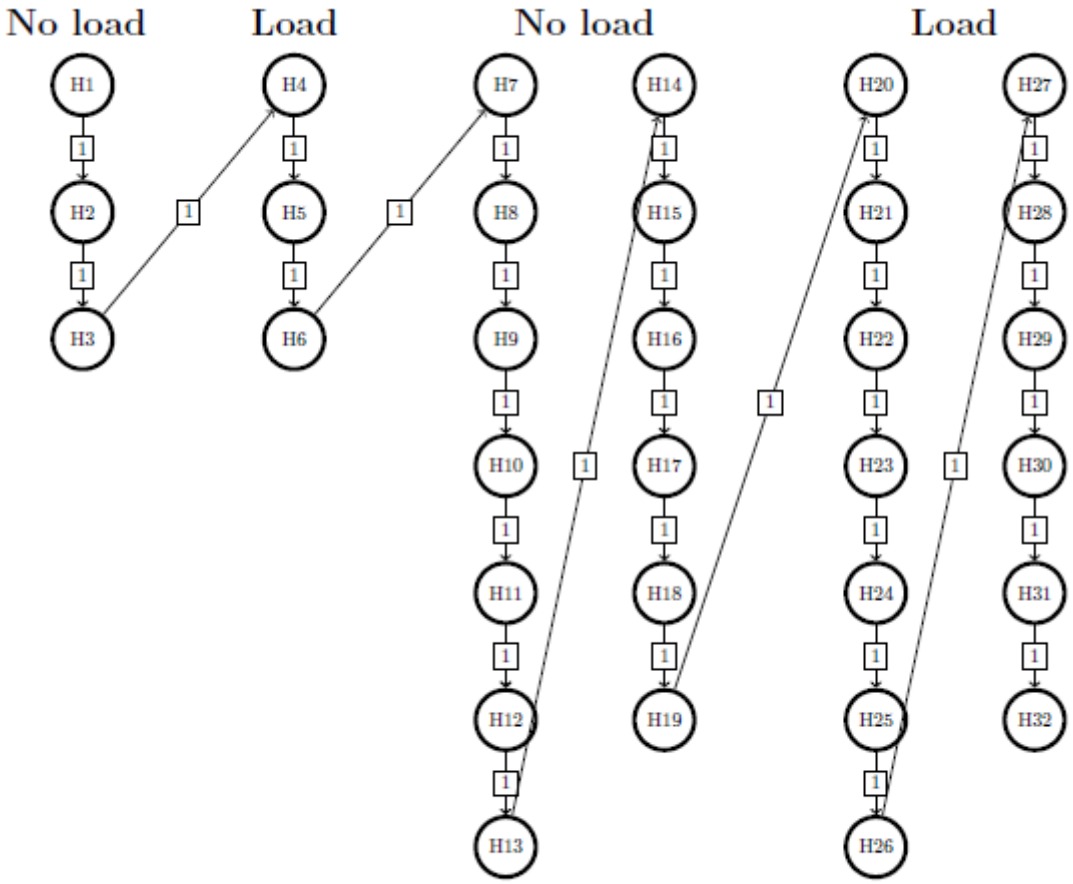
H_{29}: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from screening in SI joint edema on MRI at Week 16

H_{30}: secukinumab 150 mg (with load) is not different to placebo regimen with respect to ASDAS-CRP ID at Week 52

H_{31}: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from baseline in ASQoL at Week 52

H_{32}: secukinumab 150 mg (with load) is not different to placebo regimen with respect to change from screening in SI joint edema on MRI at Week 52

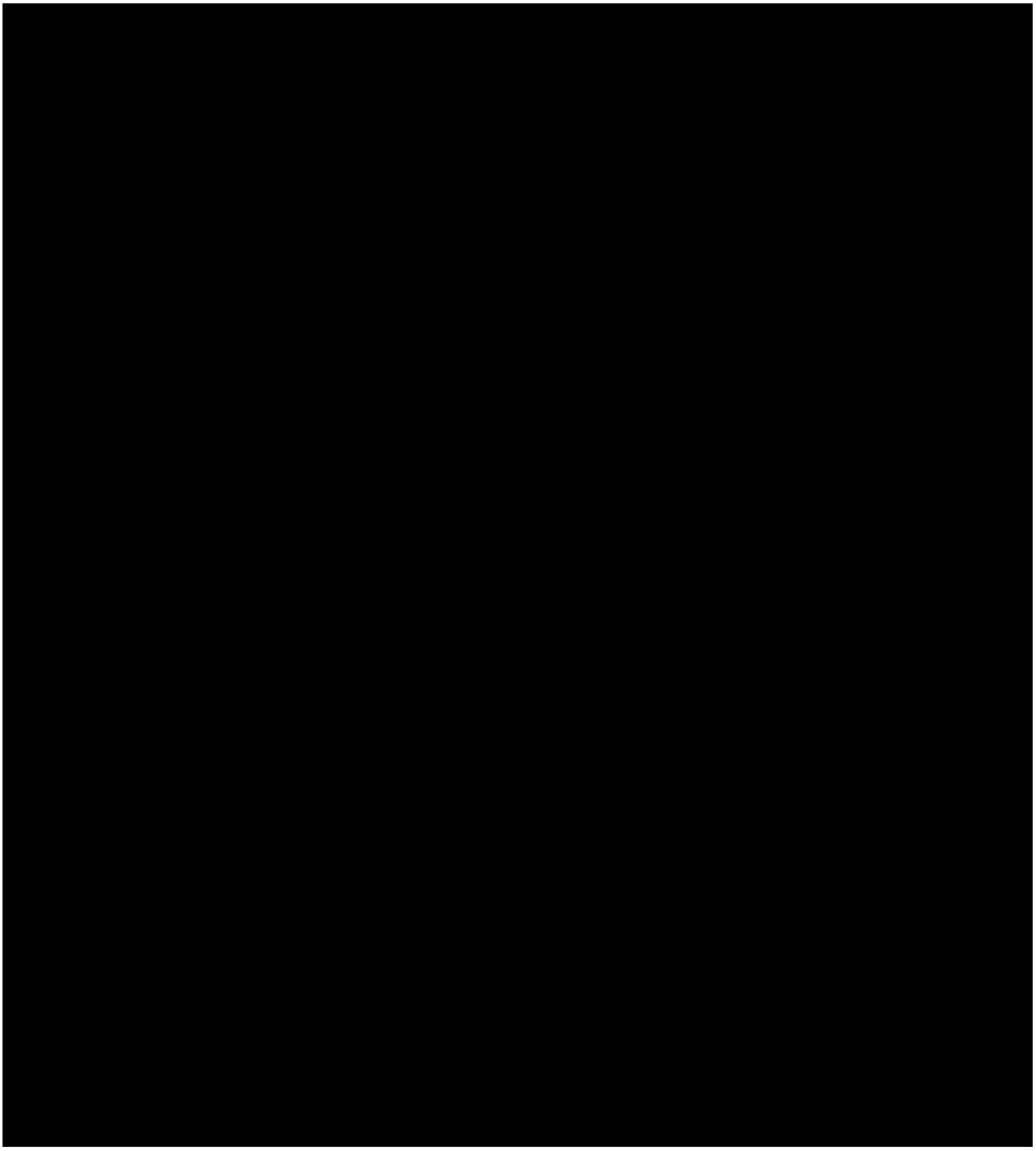
Figure 9-2 Testing strategy for analysis plan B

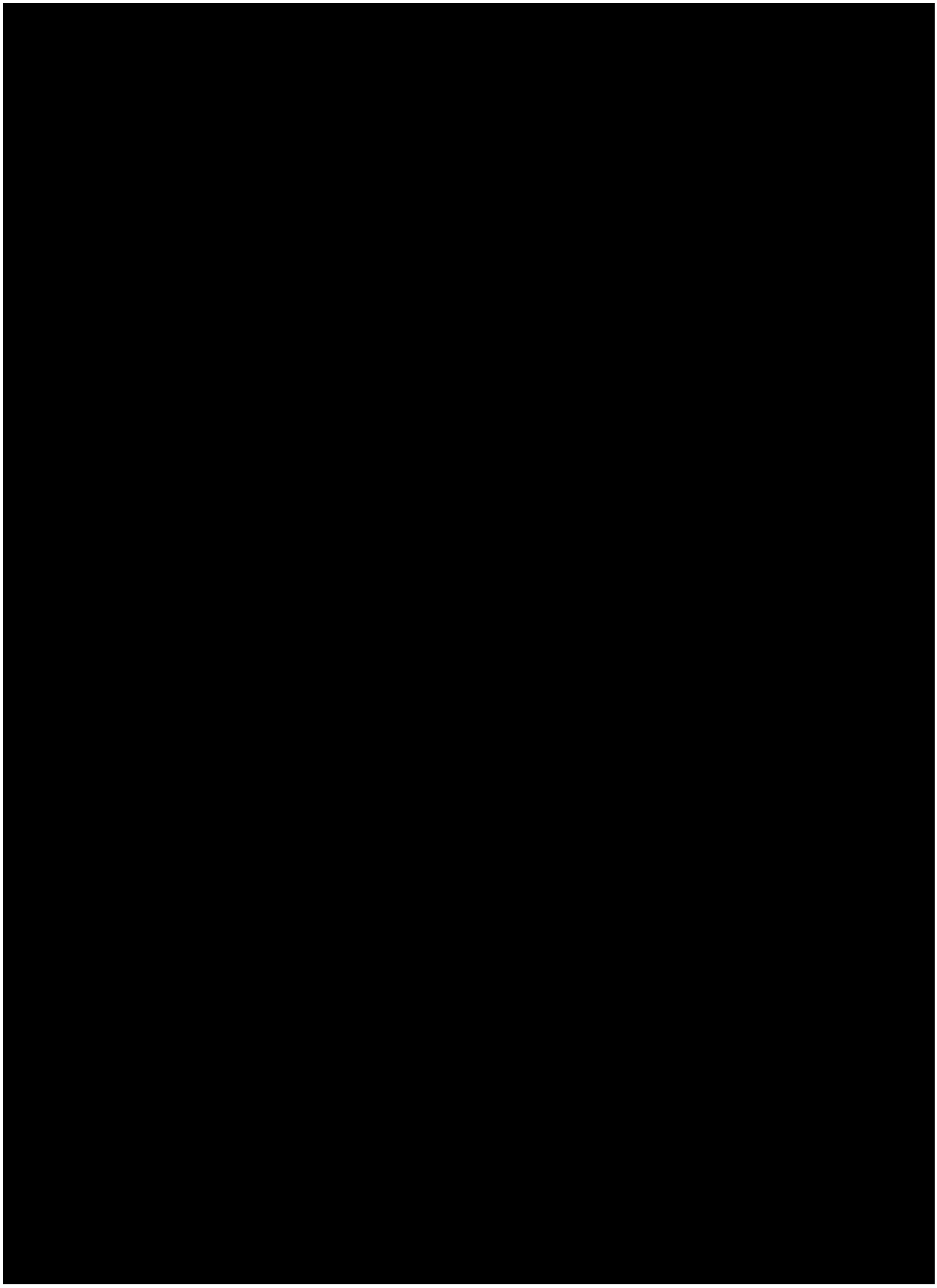


The family-wise error will be set to α=5% and it will be controlled with the proposed sequential testing strategy as described in Figure 9-2. The primary hypothesis (H_1) for the primary objective (ASAS40 in TNF naïve at Week 52) for secukinumab without load regimen versus placebo will be tested at α-level. 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_{32} 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 graphical procedure for the test of another hypothesis if the treatment effect is in favor of secukinumab.





[redacted]

9.5.3 Safety variables

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 patients 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 patient reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

These summaries may be presented separately by different study periods, e.g., Week 1-20 and entire treatment period.

As appropriate, the incidence of AEs will be presented per 100 patient years of exposure.

Separate summaries will be provided for death, serious adverse event, adverse events leading to discontinuation and adverse events leading to dose adjustment.

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 listing of those types of events as reported by the investigator and confirmed by adjudication will be provided.

Non-treatment emergent AEs will be provided in listings.

Laboratory data

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

Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for patients with both baseline and post-baseline values.

ECG

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

9.5.4 Health-related Quality of Life

Health-related Quality of Life assessments will be evaluated based on FAS unless otherwise specified.

SF-36

The following variables will be evaluated:

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

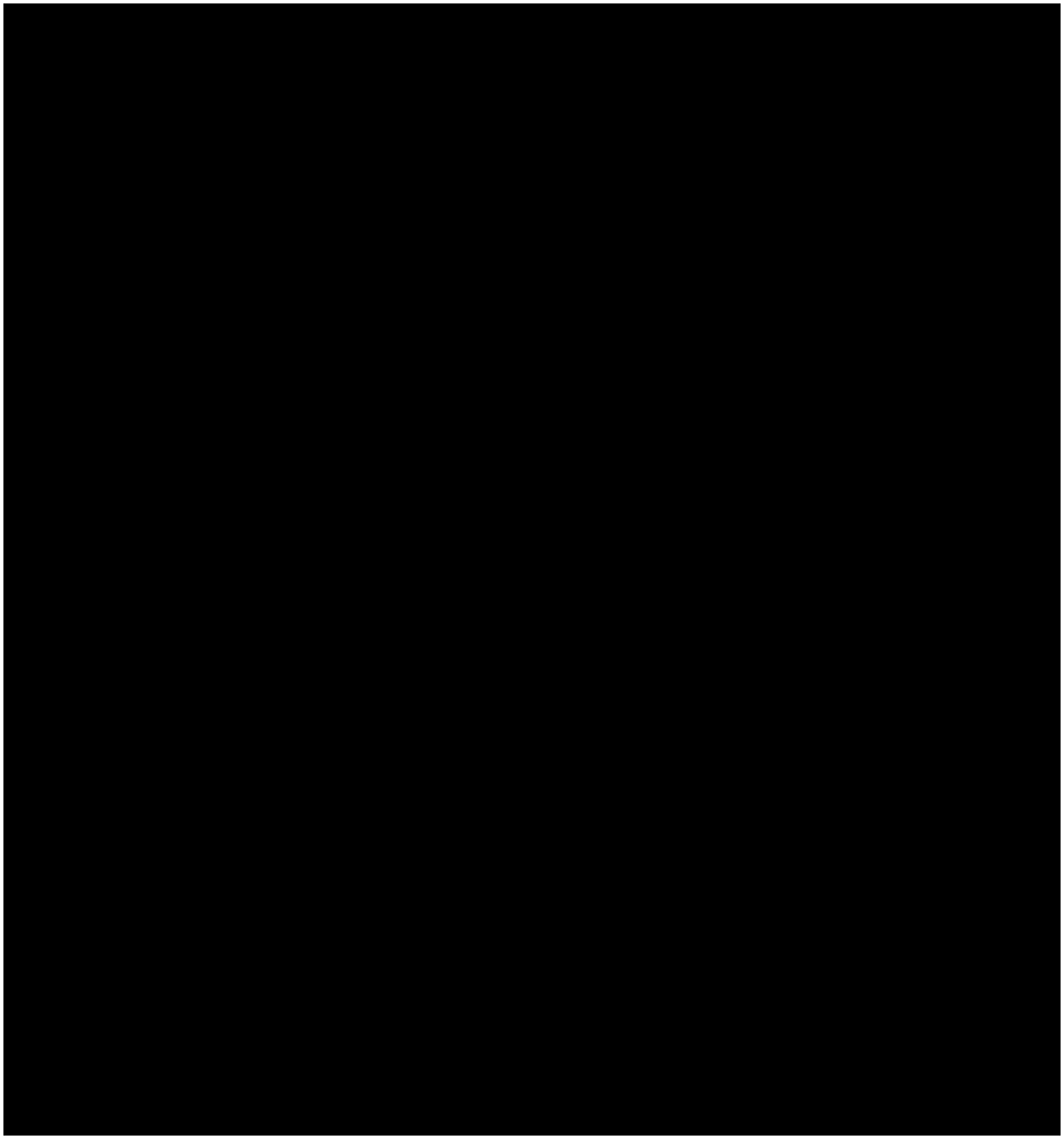
For the change in SF-36 summary scores (PCS and MCS), between-treatment differences will be evaluated using MMRM. Treatment group, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+), TNF-α status and analysis visit will be included as categorical factors and baseline SF-36 score (PCS or MCS) and weight as continuous covariates. Treatment by analysis visit and baseline SF-36 score (PCS or MCS) by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. Pairwise comparisons will be performed between secukinumab regimens and placebo and/or secukinumab at appropriate analysis visits.

In the responder analyses, treatment groups will be compared with respect to response to treatment using a logistic regression model with treatment, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+), TNF-α status as factors and baseline SF-36 score (PCS or MCS) and weight as covariates. Odds ratios and 95% CI will be presented for appropriate treatment comparisons.

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

ASQoL

For the change in ASQoL scores, between-treatment differences in the change in ASQoL scores will be evaluated using MMRM. Treatment group, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+), TNF-α status and analysis visit be used as categorical factors and baseline ASQoL score and weight as continuous covariates. Treatment by analysis visit and baseline ASQoL score by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. The significance of the treatment effects for secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo and/or secukinumab at the appropriate analysis visits.



[redacted]

9.5.8 PK/PD

Not applicable.

9.6 Interim analyses

For analysis plan A

The primary endpoint analysis will be performed after all patients complete Week 24 in order to support regulatory filing. As all patients will have completed the assessments associated with the primary endpoint (Week 16), no adjustment will be made to the type I error rate for this analysis.

Subsequent to the primary endpoint analysis, an analysis of the full double-blind treatment period (up to Week 52) will also be performed after all patients have completed the Week 52 visit.

For analysis plan B

The primary endpoint analysis will be performed after all patients complete Week 52 in order to support regulatory filing. As all patients will have completed the assessments associated with the primary endpoint (Week 52), no adjustment will be made to the type I error rate for this analysis. Based on enrollment, it is estimated that approximately 70% of patients will have completed the Week 52 assessments at the time of the database lock for Week 24 (analysis plan A). An interim analysis may be conducted at that time for analysis plan B using an Obrien-Fleming spending function to control the type I error. The results of the interim analysis will not affect the study conduct; i.e., all patients will continue to be treated according to the current study design and a blinded study team will oversee the trial conduct to prevent bias until the Week 52 database lock. Performing the interim analysis is dependent on health authority feedback and further details will be included in the statistical analysis plan, which will be finalized before Week 24 database lock.

9.7 Sample size calculation

In a study of an anti-TNF agent in the same indication of similar design (Landewé et al 2014) an ASAS40 response rate of 47.1% for active treatment and 16% for placebo was observed at Week 12; however, this trial had a limited number of TNF-IR patients and a meta-analysis (MA) from unpublished studies with secukinumab in AS indicates that the placebo rates observed in recent AS studies may be higher. Hence, assumptions are based on the result of active treatment

from this TNF-inhibitor study in nr-axSpA (but adjusted for the expected inclusion of TNF-IR patients) and with placebo response rates taken from the secukinumab MA. This MA included approximately 25% TNF-IR patients, and the ASAS40 response rate in the 150 mg dose for TNF-IR was 76% of the response in the TNF naïve group. Assuming 20% of randomized patients will be TNF-IR and have the same TNF-IR vs. TNF naïve response ratio as seen in the MA (76%), the estimate for the entire population is 44.8% (i.e. 47.1%*0.8 + 47.1%*0.2*0.76) for secukinumab and 25.9% for placebo. ASAS40 in TNF naïve patients only is assumed to be 47.1% for secukinumab and 27.9% for placebo.

At Week 16, response rates for the secukinumab 150 mg s.c. regimens with loading and without loading are assumed to be the same.

Primary endpoint for analysis plan A

An overall type I error (2-sided) 5% will be used to control type I error. Since the hierarchy is sequential starting with secukinumab with load tested versus placebo the full type I error will be utilized for each comparison.

Table 9-1 Summary of power for binary primary endpoint

Endpoint	Placebo Response Rate	Secukinumab with load		Secukinumab without load	
		Response Rate	Power N=185/arm	Response Rate	Power N=185/arm
ASAS40 TNF naïve at Week 16	27.9%	47.1%	91%	47.1%	91%

Based on these assumptions including 185 patients per arm would give 91% power to reject a hypothesis of equal response rate based on Fisher's exact test.

Primary endpoint for analysis plan B

An overall type I error (2-sided) 5% will be used to control type I error. Since the hierarchy is sequential starting with secukinumab without load tested versus placebo the full type I error will be utilized for each comparison.

Based on an assumption that the ASAS40 TNF naïve response rate at Week 16 will be 47.1% for secukinumab and 27.9% for placebo, that 80% of secukinumab patients and 65% of placebo patients will retain their response status from Week 16, and that 10% of secukinumab patients and 5% of placebo patients will be new responders at Week 52, the ASAS40 response rate at Week 52 based on non-responder imputation can be estimated as 43.0% and 21.7%, respectively, resulting in a power of 97% to reject an hypothesis of equal response rate at the 5% level.

Table 9-2 Summary of power for binary primary endpoint

Endpoint	Placebo Response Rate	Secukinumab with load		Secukinumab without Loading	
		Response Rate	Power N=185/arm	Response Rate	Power N=185/arm
ASAS40 TNF naïve at Week 52	21.7%	43.0%	97%	43.0%	97%

9.8 Power for analysis of secondary variables

Secondary endpoints for analysis plan A

In Table 9-3 the power for rejecting each of the binary secondary hypotheses at Week 16 is presented based on Fisher's exact test with a 2-sided 5% type I error rate and 185 patients per group assuming the response rates without load are the same as for with load.

Table 9-3 Power for binary secondary variables at Week 16

Endpoint	Placebo Response Rate	Secukinumab with load		Secukinumab without load	
		Response Rate	Power N=185/arm	Response Rate	Power N=185/arm
ASAS40	25.9%	44.8%	96%	44.8%	96%
ASAS5/6	24.3%	45.0%	98%	45.0%	98%
BASDAI50	19.4%	45.4%	99%	45.4%	99%
ASAS20	43.7%	61.1%	90%	61.1%	90%
ASAS PR[1]	8.7%	21.9%	93%	21.9%	93%

Source: Active from R Landewé et al 2014 (Week 12 result, 400 mg Q4W) adjusted for TNF-IR and Placebo from a meta-analysis of unpublished Novartis AS studies (CAIN457F2314 and CAIN457F2320). Calculations based on Fisher's exact test (nQuery 7.0 PTT2-1)

[1]Week 16 response for TNF naïve patients assumed 25% for secukinumab and 10% for placebo which were then adjusted for 20% TNF-IR.

In Table 9-4 the power for rejecting each of the secondary hypotheses at Week 16 based on continuous variables are presented with assumed change from baseline and standard deviation (SD). Following the assumption for response variables the change from baseline was adjusted for inclusion of TNF-IR patients but with unchanged SD. The change from baseline without load is assumed the same as for with load.

Table 9-4 Power for continuous secondary variables at Week 16

Endpoint	Common SD	Placebo Mean	Secukinumab with load		Secukinumab without load	
			Mean	Power N=185/arm	Mean	Power N=185/arm
BASDAI[1]	2.3	-1.75	-3.30	99%	-3.30	99%
hsCRP[2]	0.867	0.095	-0.544	99%	-0.544	99%
BASFI[1]	2.1	-1.37	-2.20	96%	-2.20	96%
MRI SI joint edema[3]	2.17	-0.17	-1.30	99%	-1.30	99%
SF-36 PCS[4]	7.15	3.67	6.32	94%	6.32	94%
ASQoL[4]	4.55	-2.32	-4.10	96%	-4.10	96%

SD=standard deviation. Result is mean change from baseline with CRP in log scale.

[1] Active from R Landewé et al 2014 (Week 12 result, 400 mg Q4W) adjusted for TNF-IR and Placebo from a meta-analysis of unpublished AS studies (CAIN457F2314 and CAIN457F2320).

[2] Meta-analysis of unpublished Novartis AS studies (CAIN457F2314 and CAIN457F2320)

[3] Novartis AS study (AIN457F2305)

[4] Meta-analysis of Novartis AS studies (CAIN457F2310 and CAIN457F2320)

Calculations based on two-sample t-test (nQuery 7.0 MTT0-1)

Secondary endpoints for analysis plan B

Response rates for load and without load at Weeks 16 and 52 are assumed to be the same.

Table 9-5 Power for binary secondary variables

Endpoint	Placebo Response Rate	Secukinumab with load		Secukinumab without load	
		Response Rate	Power N=185/arm	Response Rate	Power N=185/arm
ASAS40 wk52	20.5%	41.4%	99%	41.4%	99%
ASAS40 wk16	25.9%	44.8%	96%	44.8%	96%
BASDAI50 wk16	19.4%	45.4%	99%	45.4%	99%
BASDAI50 wk52	16.6%	41.8%	99%	41.8%	99%
ASAS5/6 wk16	24.3%	45.0%	98%	45.0%	98%
ASAS20 wk16	43.7%	61.1%	90%	61.1%	90%
ASDAS ID wk52[1]	10.2%	25.3%	96%	25.3%	96%

Week 16

Source: Active from R Landewé et al 2014 (Week 12 result, 400 mg Q4W) adjusted for TNF-IR and Placebo from a meta-analysis of unpublished Novartis AS studies (CAIN457F2314 and CAIN457F2320).

Week 52

Estimates from Week 16 were adjusted for assumed response retention.

[1] Week 16 response for TNF naïve patients assumed 25% for secukinumab and 10% for placebo which were then adjusted for 20% TNF-IR and assumed response retention.

ASDAS ID = ASDAS CRP Inactive Disease (ASDAS-CRP score < 1.3)

Calculations based on Fisher's exact test (nQuery 7.0 PTT2-1)

Table 9-6 Power for continuous secondary variables

Endpoint	Common SD	Placebo Mean	Secukinumab with load		Secukinumab without load	
			Mean	Power N=185/arm	Mean	Power N=185/arm
BASDAI wk16[1]	2.30	-1.75	-3.30	99%	-3.30	99%
hsCRP wk16[2]	0.867	0.095	-0.544	99%	-0.544	99%
SF-36 PCS wk16[3]	7.15	3.67	6.32	94%	6.32	94%
BASFI wk16[1]	2.10	-1.37	-2.20	96%	-2.20	96%
MRI SI joint edema wk16[4]	2.17	-0.17	-1.30	99%	-1.30	99%
ASQoL wk16[3]	4.55	-2.32	-4.10	96%	-4.10	96%

SD=standard deviation. Result is mean change from baseline with CRP in log scale.

Week 16

[1]Active from R Landewé et al 2014 (Week 12 result, 400 mg Q4W) adjusted for TNF-IR and Placebo from a meta-analysis of unpublished Novartis AS studies (CAIN457F2314 and CAIN457F2320).

[2]Meta-analysis of unpublished Novartis AS studies (CAIN457F2314 and CAIN457F2320)

[3]Meta-analysis of Novartis AS studies (CAIN457F2310 and CAIN457F2320)

[4]Novartis AS study (CAIN457F2305).

Calculations based on two-sample t-test (nQuery 7.0 MTT0-1)

Power for continuous composite estimands depends on the difference in continuous endpoint and difference in treatment escape rates. Assuming the change from baseline being the same at Week 52 as at Week 16 and no escape, the power for Wilcoxon rank sum test would be similar to power of two-sample t-test (ASQoL 96% and MRI SI joint edema 99%). If escape rates are similar in both treatment arms the power will decrease if overall escape rate is increasing, whereas the power will remain the same or increase if escape rates are different between treatment arms.

9.9 Analysis of extension phase

The analysis extension phase data will be exploratory in nature and mainly reported by descriptive statistics, applying the same principles as in core phase data analysis.

Statistical models may be applied to produce confidence intervals for treatment summaries, but no formal statistical inference will be done.

Data analyses will be presented by treatment groups. Treatment groups for core phase responders are as follows:

- Secukinumab 150 mg blinded
- Secukinumab 300 mg blinded

and for core phase non-responders:

- Secukinumab 300 mg open-label

The following analysis sets will be used in the extension phase:

Full analysis set (FAS): The FAS will be comprised of all subjects enrolled in the extension phase.

Safety set: The safety set includes all subjects enrolled in the extension phase and who took at least 1 dose of study treatment during the extension phase

Total sample size for extension phase is not pre-specified. It is estimated that approximately 70% of subjects enrolled in the core phase will enter the extension phase, which is equivalent to about 380 subjects. Around 305 subjects are estimated to be core phase responders and will be in the randomized group and around 75 subjects are expected to be core phase non-responders and will enter the open-label treatment group.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the entire study or longer if required by locally approved prescribing information (e.g. 20 weeks in EU). If there is any question that the patient will not reliably comply, they should not be entered in the study.

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In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

10.3 Responsibilities of the investigator and IRB/IEC

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

10.4 Publication of study protocol and results

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

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

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

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring should be followed.

12 References

References are available upon request

Baraliakos X and Braun J (2011) Spondyloarthritides. Best Pract Res Clin Rheumatol; 25:825-42.

Baraliakos X, Braun J, Laurent D, et al (2011) Interleukin-17A blockade with secukinumab reduces spinal inflammation in patients with ankylosing spondylitis as early as Week 6, as detected by Magnetic Resonance Imaging. Arthritis Rheum; 63:S972.

Baraliakos X, Listing J, Brandt J, et al (2005) Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. Arthritis Res Ther; 7: R439-R444.

[redacted]

Callhoff J, Sieper J, Weib A,et al (2014) Efficacy of TNFα blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. Ann Rheum Dis; 0:1-8

[redacted]

Dougados M, van der Heijde D, Sieper J, et al (2013) Safety and Efficacy Of Etanercept In Early Non-Radiographic Axial Spondyloarthritis: A Randomized, Double-Blind, Placebo-Controlled Trial At 24 Weeks. Abstract Number 1516. ACR 2013

Dougados M, van der Heijde D, Sieper J, et al (2014) Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis – a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum; 66:2091-2102.

EMA guidance document:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003424.pdf

[redacted]

Huffman KM, Samsa GP, Slentz CA, et al (2006) Response of high-sensitivity C-reactive protein to exercise training in an at-risk population. Am Heart J; 152:793-800.

Koch GG, Tangen CM, Jung JW, et al (1998) Issues for covariance analysis of dichotomous and ordered categorical data from randomized clinical trials and non-parametric strategies for addressing them. Statist Med; 17:1863-92.

Landewé R, Braun J, Deodhar A, et al (2014) Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomized placebo-controlled Phase 3 study. Ann Rheum Dis; 73:39-47.

Langley RG, Elewski BE, Lebwohl M, et al (2014) Secukinumab in plaque psoriasis–results of two phase 3 trials. N Engl J Med; 371(4):326–38.

Lubeck DP (2004) Patient-reported outcomes and their role in the assessment of rheumatoid arthritis. Pharmacoeconomics; 22 Suppl 1:27-38.

Lukas C, Landewé R, Sieper J, et al (2009) Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis; 68:18-24.

Machado P, Landewé R, Lie E, et al (2011) Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis; 70:47-53.

McHorney CA, Ware JE and Raczek AE C (1992) The MOS 36-Item Short-Form Health Survey (SF-36). Medical Care; 31: 247-263.

Mease PJ, McInnes IB, Kirkham B, et al (2015) Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med; 373(14):1329-39.

Mettler FA, Huda W, Yoshizumi TT, et al (2008) Effective doses in Radiology and Diagnostic Nuclear Medicine – A catalog. Radiology; 248:254-63.

Pavy S, Brophy S, Calin A (2005) Establishment of the minimum clinically important difference for the Bath Ankylosing Spondylitis Indices- A prospective study. J Rheumatol; 32:80-5.

Poddubnyy D, Rudwaleit M, Haibel H, et al (2011) Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. Ann Rheum Dis; 70:1369-74.

Robinson PC, Wordsworth BP, Reveille JD, et al (2013) Axial spondyloarthritis: a new disease entity, not necessarily early ankylosing spondylitis. Ann Rheum Dis; 72:162-4.

Rudwaleit M, Landewé R, van der Heijde D, et al (2009) The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis; 68:770-76.

Sieper J, Rudwaleit M, Baraliakos X, et al (2009) The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis; 68 Suppl 2:1-44.

Sieper J (2012) Developments in therapies for spondyloarthritis. Nat Rev Rheumatol; 8:280-87.

Sieper J, Kivitz AJ, Van Tubergen AM, et al. (2012) Rapid improvements in patient reported outcomes with certolizumab pegol in patients with axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis: 24 week results of a phase 3 double blind randomized placebo-controlled study. Abstract Number 558. ACR 2012

Sieper J and van der Heijde D (2013) Nonradiographic Axial Spondyloarthritis - New Definition of an Old Disease? Arthritis Rheum; 65:543-51.

Sieper J, van der Heijde D, Dougados M, et al (2013) Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis; 72:815-22.

Song IH, Hermann KG, Haibel H, et al (2011) Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomized controlled trial. Ann Rheum Dis; 70:590-96.

Song IH, Weib A, Hermann KG, et al (2013) Similar response rates in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis after 1 year of treatment with etanercept: results from the ESTHER trial. Ann Rheum Dis; 72:823-25.

Stabin M, Marcus C, Siegel J (2009) New tool for nuclear medicine patient release calculations. J Nucl Med; 50:14N.

US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) (2013) Guidance for Industry – Electronic Source Data in Clinical Investigations.

van der Heijde D, Landewé R, Baraliakos X, et al (2008a) Radiographic findings following two years of infliximab therapy in patients with Ankylosing Spondylitis. Arthritis Rheum; 58:3063-70.

van der Heijde D, Landewé R, Einstein S, et al (2008b) Radiographic progression of Ankylosing Spondylitis after up to two years of treatment with etanercept. Arthritis Rheum; 58:1324-31.

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

van Tubergen A, Black PM, Coteur G (2015) Are patient-reported outcome instruments for ankylosing spondylitis fit for purpose for the axial spondyloarthritis patient? A qualitative and psychometric analysis. Rheumatology; EPub

Wallis D, Haroon N, Ayearst R, et al (2013) Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis: Part of a Common Spectrum or Distinct Diseases? J Rheumatol; 40:2038-41.

Ware JE and Donald Sherbourne C (1992) The MOS 36-Item Short-Form Health Survey (SF-36). Medical Care; 30: 473-483.

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13 Appendices

13.1 Appendix 1: Clinically notable laboratory values

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

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

Table 13-1 Safety Analyses: Expanded Limits and Notable Criteria

Laboratory Variable	Final Harmonization Notable Criteria	
	Standard Units	**SI Units**
LIVER FUNCTION AND RELATED VARIABLES		
SGOT (AST)	>3 x ULN	>3 x ULN
SGPT (ALT)	>3 x ULN	>3 x ULN
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	

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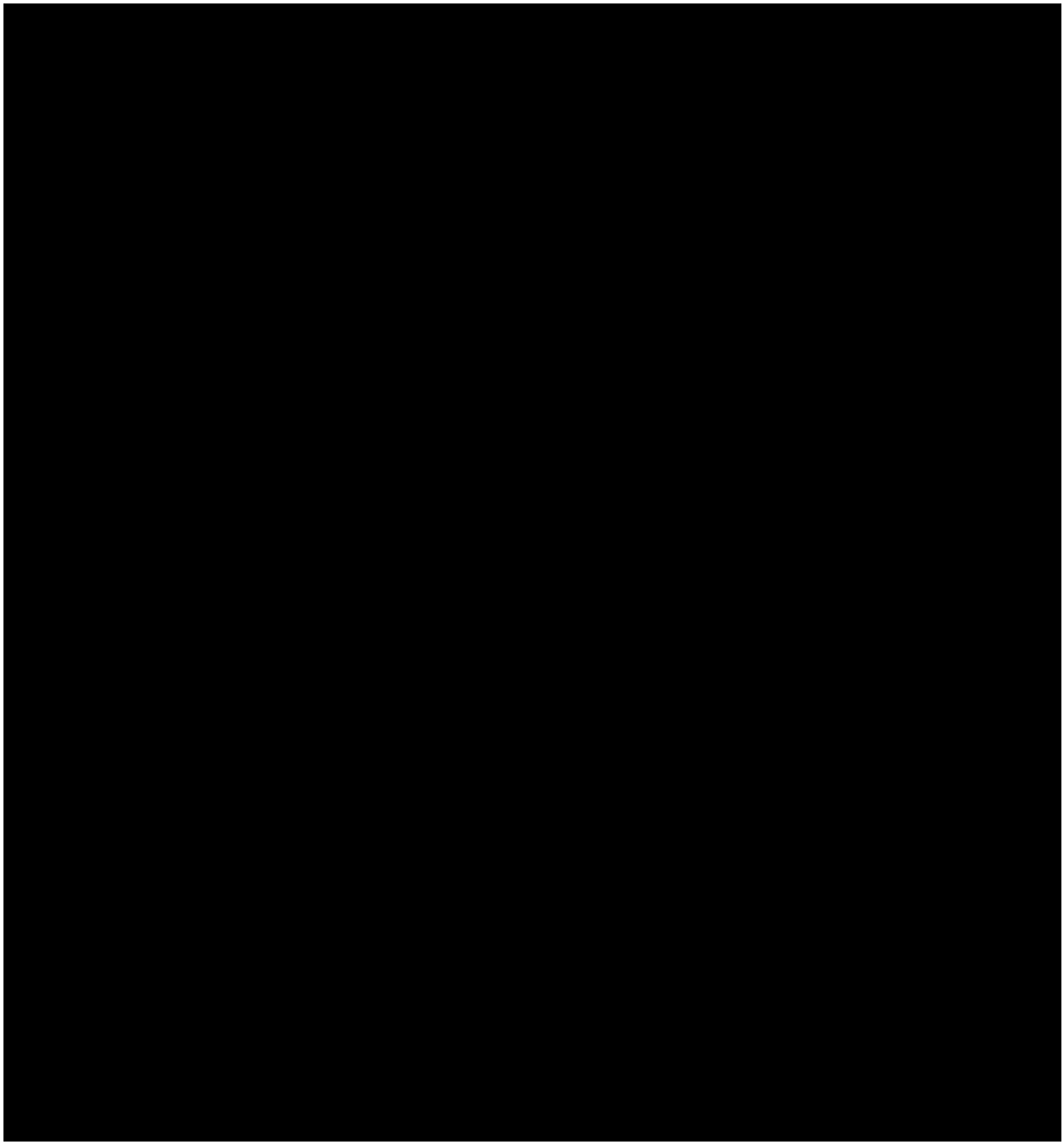


13.3 Appendix 3: Modified New York criteria

According to Exclusion Criteria 1, patients must not have below described radiological changes

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.

13.4 Appendix 4: ASAS Classification Criteria for Axial Spondyloarthritis (axSpA)

In patients with ≥ 3 months back pain and age at onset <45 years:

Sacroiliitis on imaging* plus ≥ 1 SpA feature	OR	HLA-B27 plus ≥ 2 other SpA features

*Sacroiliitis on imaging:
- Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- Definite radiographic sacroiliitis according to the modified NY criteria

SpA features:
- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's / colitis
- Good respons to NSAIDs
- Family history for SpA
- HLA-B27
- Elevated CRP

13.5 Appendix 5: Assessment of SpondyloArthritis International Society criteria (ASAS)

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

Main ASAS domains:

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

Additional assessment domains:

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

13.5.1 Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those patients with AS. The ten questions were chosen with a major input from patients with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions

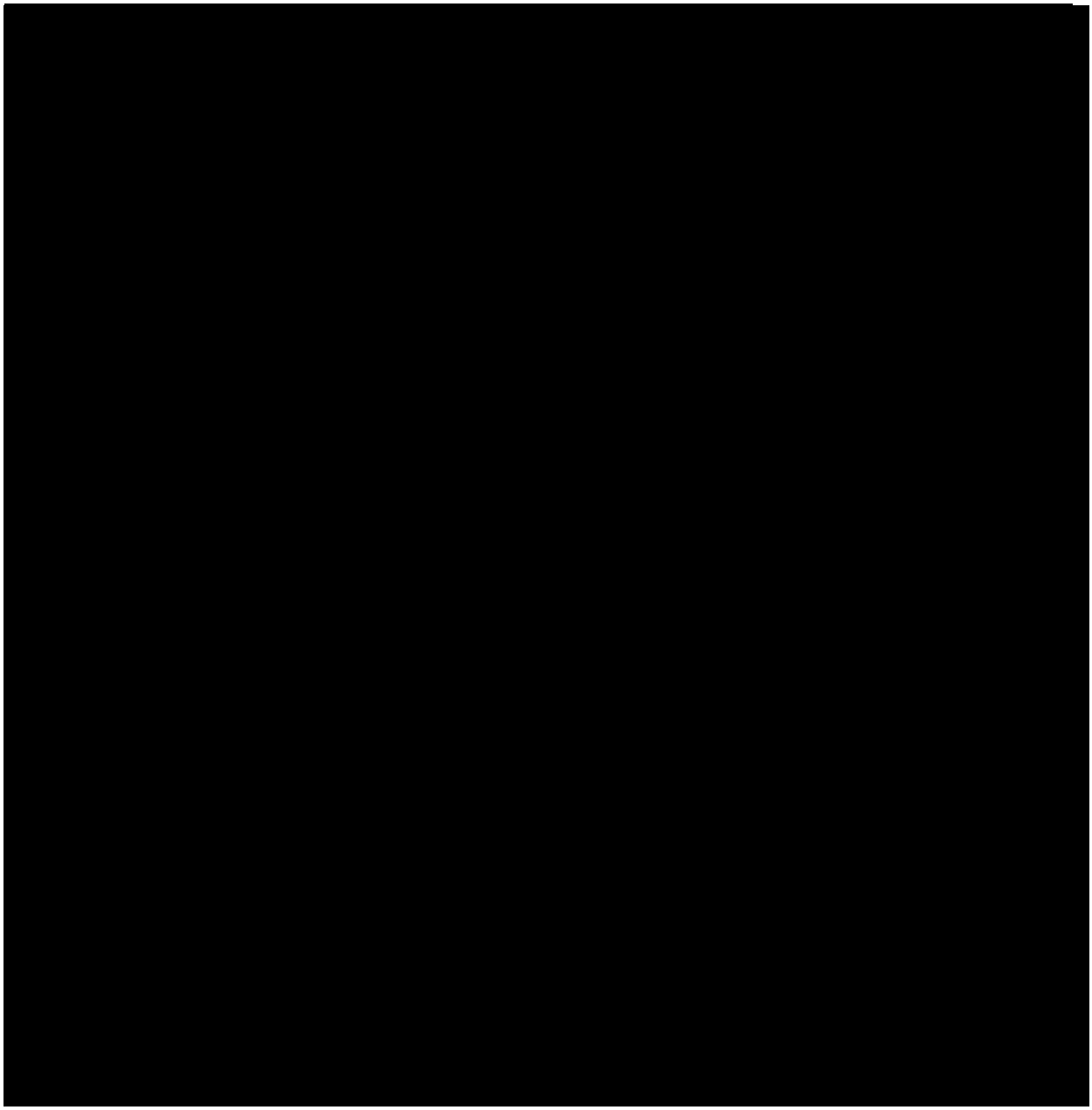
assess the patients' ability to cope with everyday life. A 10 cm visual analog scale is used to answer the questions. The mean of the ten scales gives the BASFI score – a value between 0 and 10.

13.5.2 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

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

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

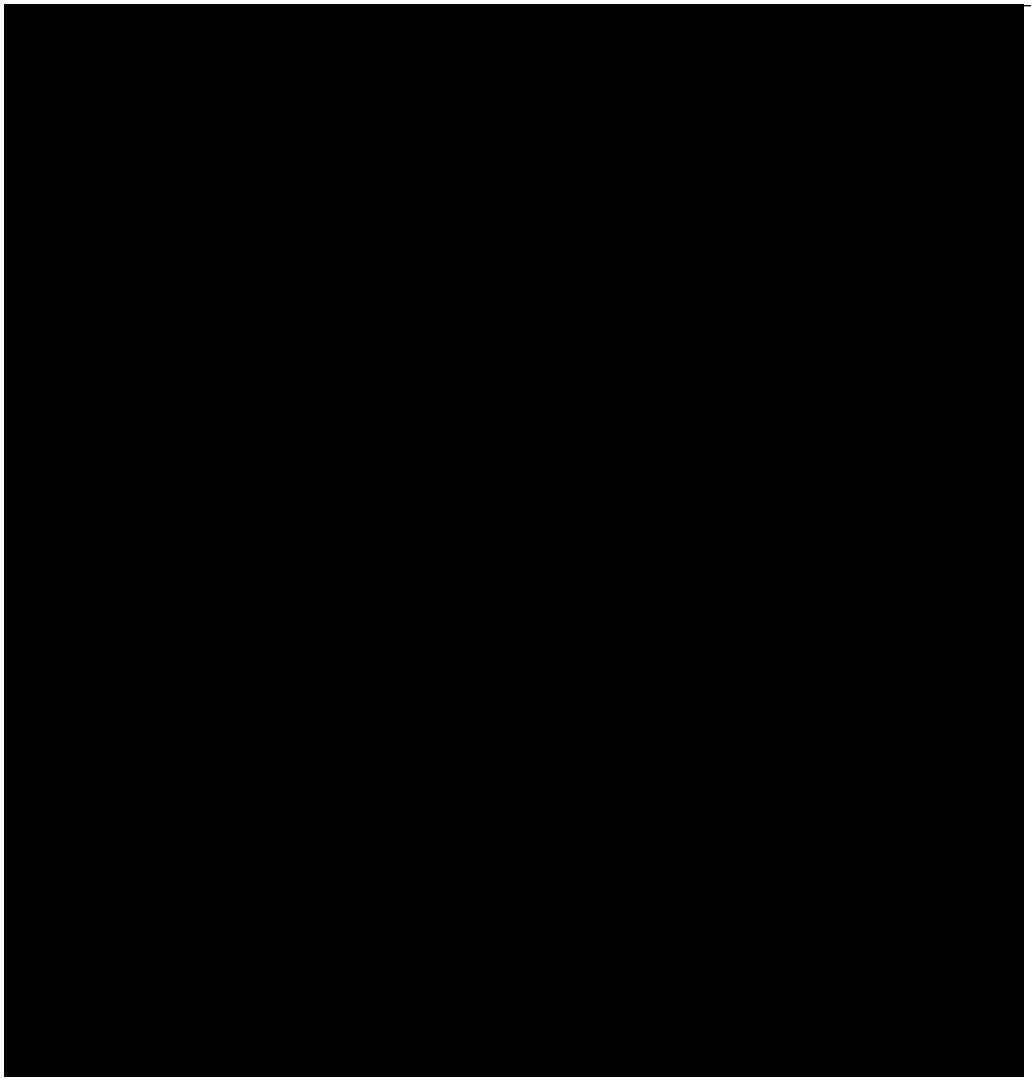
To give each symptom equal weighting, the mean (average) of the two scores relating to morning stiffness (questions 5 and 6) is taken. The mean of questions 5 and 6 is added to the scores from questions 1-4. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score. Scores of 4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



13.6 Appendix 6: Definition of Sacroiliitis on MRI

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

- The presence of definite subchondral bone marrow oedema/osteitis highly suggestive of sacroiliitis is mandatory.
- The presence of synovitis, capsulitis, or enthesitis only without concomitant subchondral bone marrow oedema/osteitis is compatible with sacroliitis but not sufficient for making a diagnosis of active sacroliitis.
- Amount of signal required: if there is one signal (lesion) only, this should be present on at least two slices. If there is more than one signal on a single slice, one slice may be enough.



13.8 Appendix 8: Guidelines for administering the questionnaires for patient reported outcomes

Before trial start

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

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

Before completion

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

During completion

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

After completion

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

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

Addressing problems and concerns

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

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

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

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

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

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

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

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

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

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

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

The patient asks the meaning of a question/item

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

General information about all questionnaire(s):

All questionnaires have to be completed by the patients in their local languages 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.