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AIN457

Clinical Trial Protocol CAIN457I2301 / NCT04732117

A randomized, double-blind, placebo controlled, multicenter, phase III study of subcutaneous secukinumab to compare efficacy at 16 weeks with placebo and to assess safety and tolerability up to 52 weeks in Chinese participants with active non-radiographic axial spondyloarthritis.

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AS	Ankylosing Spondylitis
ASAS	Ankylosing SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASDAS-MI	Ankylosing Spondylitis Disease Activity Score-Major Improvement
ASQoL	Ankylosing Spondylitis Quality of Life
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
axSpA	Axial Spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
[redacted]	[redacted]
bDMARDs	biologic disease-modifying anti-rheumatic drugs
BMI	Body Mass Index
BSL	Baseline
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulation
CI	Confidence Interval
CMO&PS	Chief Medical Office and Patient Safety
COA	Clinical Outcome Assessment
COVID-19	Coronaviruses 2019
COX	Cyclooxygenase
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP (hsCRP)	(high sensitivity) C-reactive protein
CRP+	Patient with a CRP value above the ULN at screening
csDMARDs	(conventional synthetic) Disease Modifying Anti-Rheumatic Drugs
CSR	Clinical Study Report
CT	Computed Tomography
CXCL	Chemokine (C–X–C motif) ligand
DDE	Detailed Design Enhancement
DMARD	Disease modifying anti-rheumatic drug
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EDD	Expected Delivery Date
ELISA	Enzyme-linked immuno sorbent assay
EMA/EMEA	European Medical Agency
EOS	End of Study
EOT	End of Treatment
eSource	Electronic Source

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[redacted]	[redacted]
EU	European Union
EULAR	European League Against Rheumatism
FAS	Full analysis set
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	Hour
hCG	Human Chorionic Gonadotropin
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
hsCRP	(high sensitivity) C-Reactive Protein
IB	Investigator's Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFU	Instructions for Use
IgG	Immunoglobulin G
IL	Interleukin
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
LDH	lactate dehydrogenase
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
MAR	Missing at Random
[redacted]	[redacted]
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
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
MTX	Methotrexate
NDA	New Drug Application
NMPA	National Medical Products Administration
nr-axSpA	Non-radiographic axial spondyloarthritis
NSAID	Non-steroidal anti-inflammatory drug
PCS	Physical Component Summary
PDD	Purified Protein Derivative
PFS	Pre-filled syringe
PK	Pharmacokinetic(s)
PRN	Pro re nata
PRO	Patient Reported Outcomes
PsA	Psoriatic arthritis

[redacted]

QMS	Quality Management System
QoL	Quality of life
RA	Rheumatoid Arthritis
RBC	red blood cell(s)
s.c.	Subcutaneous
SAA	Spondylitis Association of America
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SF-36	Short Form-36
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SIJ/SI Joint	Sacroiliac Joint
SpA	Spondyloarthritis
SPARTAN	Spondyloarthritis Research and Treatment Network
SUSAR	Suspected Unexpected Serious Adverse Reaction
t.i.d	ter in die, three times a day
TB	Tuberculosis
TNFα-IR	TNFα inhibitor inadequate responder
TNF/TNFα	Tumor Necrosis Factor
ULN	upper limit of normal
VAS	Visual analog scale
WBC	White blood cell(s)
WHO	World Health Organization

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Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 150 mg once in 4 weeks)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Epoch	A portion of the study which serves a specific purpose. Typical Epochs are: screening / wash-out, treatment, and follow-up.
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Investigational drug/ treatment	The drug whose properties are being tested in the study
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 medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned

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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.
Randomization number	A unique identifier assigned to each randomized participant
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or Electronic Source (eSource)
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

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Protocol summary

Protocol number	CAIN457I2301
Full Title	A randomized, double-blind, placebo controlled, multicenter study of subcutaneous secukinumab, to compare efficacy at 16 weeks with placebo and to assess safety and tolerability up to 52 weeks in Chinese participants with active non-radiographic axial spondyloarthritis
Brief title	Efficacy and safety study of secukinumab in Chinese participants 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 Chinese participants with active non-radiographic axial spondyloarthritis
Primary Objective(s)	To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the proportion of TNF-α naive participants achieving an ASAS40 response (Assessment of SpondyloArthritis International Society criteria).
Secondary Objectives	• To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the proportion of overall participants achieving an ASAS40 response. • To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the proportion of participants meeting the ASAS 5/6 response criteria. • To assess the efficacy of secukinumab 150 mg s.c. compared to placebo at Week 16 based on the change from baseline in total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). • To assess the efficacy of secukinumab 150 mg s.c. compared to placebo at Week 16 based on the proportion of participants achieving BASDAI 50. • To assess the efficacy of secukinumab 150 mg s.c. compared to placebo at Week 16 based on the change from baseline of high sensitivity C-Reactive Protein (hsCRP). • To assess the efficacy of secukinumab 150 mg s.c. compared to placebo at Week 16 based on the change from baseline in total Bath Ankylosing Spondylitis Functional Index (BASFI). • To assess the efficacy of secukinumab 150 mg s.c. compared to placebo at Week 16 based on the change from baseline in sacroiliac (SI) joint edema on Magnetic resonance imaging (MRI). • To assess the efficacy of secukinumab 150 mg s.c. compared to placebo at Week 16 based on the proportion of participants achieving an ASAS20 response. • To assess the efficacy of secukinumab 150 mg s.c. compared to placebo at Week 16 based on proportion of participants achieving Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease as defined by ASDAS < 1.3. • To assess the efficacy of secukinumab 150 mg s.c. compared to placebo at Week 16 based on the change from baseline in Short Form-36 Physical Component Summary (SF-36 PCS). • To assess the efficacy of secukinumab 150 mg s.c. compared to placebo at Week 16 based on the change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) scores. • To assess the efficacy of secukinumab 150 mg s.c. compared to placebo at Week 16 based on the proportion of participants achieving ASAS partial remission. • To evaluate overall safety and tolerability of secukinumab.
Study design	This is a randomized, double-blind, placebo-controlled study.

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Study population	The study population will consist of male and female participants (≥ 18 years old at the time of consent) fulfilling the ASAS classification criteria for Axial Spondyloarthritis (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 Ankylosing Spondylitis (AS).
Key Inclusion criteria	• Signed informed consent must be obtained prior to participation in the study. • Male or non-pregnant, non-lactating female participant at least 18 years of age. • Diagnosis of axSpA according to ASAS axSpA criteria: 1. Inflammatory back pain for at least 6 months 2. Onset before 45 years of age 3. Sacroiliitis on MRI (as assessed by central reader) with ≥ 1 Spondyloarthritis (SpA) feature OR HLA-B27 positive with ≥2 SpA features • Objective signs of inflammation at screening, evident by either 1. MRI with Sacroiliac Joint inflammation (as assessed by central reader AND / OR 2. hsCRP > upper limit of normal (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 Visual analog scale (VAS) ≥ 40 mm (0-100 mm) at baseline. • Participants should have been on at least 2 different Non-steroidal anti-inflammatory drug (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. • Participants who are regularly taking NSAIDs [including cyclooxygenase-1 (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. • Participants 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. • Participants who have previously been on a TNFα inhibitor will be allowed entry into study after an appropriate wash-out period prior to randomization: 1. 4 weeks for Enbrel® (etanercept) or "Yi Sai Pu", “An Bai Nuo” or “Qiang Ke” – with a terminal half-life of 102 ± 30 hours (s.c. route) 2. 8 weeks for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (i.v. infusion) 3. 10 weeks for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route) 4. 10 weeks for Simponi® (golimumab) – with a terminal half-life of 11-14 days 5. 10 weeks for Cimzia® (certolizumab) – with a terminal half-life of 14 days • Participants taking Methotrexate(MTX) (≤ 25 mg/week) or sulfasalazine (≤ 3 g/day) are allowed to continue their medication and must have taken it for at least 3 months and have to be on a stable dose for at least 4 weeks prior to randomization • Participants on MTX must be on stable folic acid supplementation before randomization • Participants 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 • Participants taking systemic corticosteroids have to be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization
Key Exclusion criteria	• Participants 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

[redacted]

	• Inability or unwillingness to undergo MRI scan (e.g., participants with pacemakers, aneurysm clips or metal fragments / foreign objects in the eyes, skin or body that are not MRI compatible) • Chest X-ray or computed tomography (CT) scan with evidence of ongoing infectious or malignant process, obtained within 3 months of screening and evaluated by a qualified physician • Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor • Any therapy by intra-articular injections (e.g., corticosteroid) within 4 weeks before randomization • Participants who have taken more than one anti-TNFα agent • 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 Non-radiographic axial spondyloarthritis(nr-axSpA)that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease or uveitis • 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(TB) infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5 mm or according to local practice/guidelines) or a positive QuantiFERON TB-Gold test as indicated in the assessment schedule in Table 8-1. Participants with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the participant has no evidence of active TB. If presence of latent TB 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
Study treatment	Secukinumab 150 mg s.c. and matching placebo
Treatment of interest	The randomized treatment (either secukinumab or placebo up to Week 16 and secukinumab after Week 16) with or without the allowed concomitant medication for managing axSpA inflammatory back pain (add-on to standard of care). The dose of the allowed concomitant medication must remain stable during the trial and allowed to modify only after Week 24.
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]

Key safety assessments	● QuantiFERON TB-Gold test or PPD skin test ● Chest X-ray or CT ● 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] ● X-Ray of the sacroiliac joints [redacted]
Data analysis	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. Difference in response proportions between secukinumab regimen and placebo regimen and the corresponding 95% confidence interval (CI) will be computed utilizing the logistic regression model fitted.
Key words	Non-radiographic spondyloarthritis, chronic inflammatory disease, inflammatory back pain, secukinumab, AIN457

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1 Introduction

1.1 Background

Axial spondyloarthritis (axSpA) is a group of rheumatic disorders with spinal inflammation and inflammatory back pain as a common denominator. Patients with axSpA experience a substantial burden of disease, including pain in the sacrum, lower back, peripheral joints and tendon insertions, stiffness, decreased spinal mobility, decreased physical function, difficulty sleeping, fatigue, difficulty working, and decreased quality of life.

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 ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA). 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 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 prevalence of AS and nr-axSpA is comparable, with each occurring in 0.3% to 0.6% of the population (Reveille and Weisman 2013**),** **(**Strand et al 2013) There is no exact epidemiology data for nr-axSpA in China, the prevalence of AS in China is around 0.3% (Chinese Rheumatology Association 2010), nr-axSpA prevalence in China could be estimated to be 0.3% as comparable to AS.

AS and nr-axSpA share many common epidemiologic, genetic, and clinical characteristics (Kiltz et al 2012), (Ciurea et al 2013), (Reveille and Weisman 2013), (Song et al 2013), (Strand et al 2013), (Landewé et al 2014), (Poddubnyy and Sieper 2014), (Poddubnyy et al 2015). 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).

Disease parameters and response rates to treatment with tumor necrosis factor (TNFα) antagonists are similar in patients with AS and nr-axSpA, further supporting the concept that axSpA is a disease with distinct stages **(**Song et al 2013). Moreover, results from the C-axSpAnd trial (a 52-week, randomized, multicenter, double-blind, placebo controlled study of certolizumab pegol in nr-axSpA) showed that at Week 52, the placebo group was associated with a poor outcome (with only 7.0% of patients attaining an Ankylosing Spondylitis Disease Activity Score-Major Improvement (ASDAS-MI) vs. 47.2% in the biological disease modifying anti-rheumatic drugs (bDMARDs) treatment group (Deodhar et al 2019). This shows that nr-axSpA is a true disease that does not resolve spontaneously or improve without adequate treatment.

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered first-line therapy for all patients with axSpA. International management guidelines developed by experts in the field ((ACR/SAA/SPARTAN: (Ward et al 2016) ASAS/EULAR: (van der Heijde et al 2017)) recognize nr-axSpA and AS as viable disease entities within the spectrum of axSpA and support the use of bDMARDs for the full spectrum of axSpA.

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Anti-TNFα agents are approved therapies for patients with AS who continue to have active disease despite NSAIDs. In Europe, several anti-TNFα agents are approved for nr-axSpA with objective signs of inflammation, whereas only one anti-TNFα agent is approved in the United States. It's worth noting that no anti-TNFα agents are approved for the treatment of nr-axSpA in China.

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, TNFα 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). While effective in treating the inflammatory symptoms, TNFα antagonists have also not been shown to impact structural damage of the joints in AS beyond the level of NSAIDs in blinded cohort comparisons over 2 years of treatment (van der Heijde et al 2008). Thus, there remains an unmet medical need for new therapies.

Secukinumab (AIN457) is a high-affinity recombinant, fully human monoclonal anti-human Interleukin-17A antibody of the Immunoglobulin G (IgG1)/κ-class. Secukinumab binds to human IL-17A and neutralizes the bioactivity of this cytokine. Interleukin (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.

Secukinumab 150 mg showed very good efficacy in the two AS Phase III global pivotal studies CAIN457F2305 (MEASURE 1) and CAIN457F2310 (MEASURE 2), as well as a China-centric Phase III study CAIN457F2308 (MEASURE 5) which enrolled 327 out of 458 (71.4%) Chinese patients with active AS. Recently, secukinumab 150 mg has been approved in Europe and United States for nr-axSpA patients based on data from a global pivotal study CAIN475H2315 (PREVENT) conducted to evaluate the efficacy and safety of secukinumab 150 mg vs. placebo in patients with nr-axSpA.

Secukinumab is approved for the treatment of psoriasis and AS in China. Full safety results from completed studies show that secukinumab is generally safe and well tolerated in Chinese patients. Please refer to the AIN457 Investigator's Brochure edition 20 for a more detailed review of the risk: benefit profile of secukinumab which supports its clinical development for the treatment of nr-axSpA patients with secukinumab in China.

1.2 Purpose

The purpose of this bridging study is to evaluate efficacy, safety and tolerability of secukinumab 150 mg s.c. compared to placebo in Chinese participants with active nr-axSpA at Week 16 to support registration in China. Meanwhile, this study will also observe the long-term efficacy, safety and tolerability of secukinumab including spinal and SI-joint inflammation as evidenced by magnetic resonance imaging (MRI) at Week 52.

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Additionally, efficacy, safety and tolerability of secukinumab 300 mg s.c. will be assessed in non-responders, defined as participants who have not achieved ASAS20 at Week 24.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoints for primary objective**
● To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the proportion of TNF-α naive participants achieving an ASAS40 response (Assessment of SpondyloArthritis International Society criteria).	● ASAS40 response rate at Week 16 ASAS40 response is defined as an improvement of ≥40% and an absolute improvement from baseline of ≥2 units on a 10-point scale in at least three of the four main domains and no worsening assessed at all in the remaining domain. 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
Secondary objectives	**Endpoints for secondary objectives**
● To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the proportion of overall participants achieving an ASAS40 response.	● ASAS40 response rate in overall participants at Week 16
● To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the proportion of participants meeting the ASAS 5/6 response criteria.	● ASAS 5/6 response rate at Week 16 ASAS 5/6 response is defined as an improvement of ≥20% in at least five of all six domains.
● To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the change from baseline in total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).	● Change from baseline in total BASDAI at Week 16
● To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the proportion of participants achieving BASDAI 50.	● BASDAI 50 proportion at Week 16 BASDAI 50 is defined as an improvement of at least 50% in the BASDAI total score compared to baseline.
● To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the change from baseline of high sensitivity C-Reactive Protein (hsCRP).	● Change from baseline in hsCRP at Week 16
● To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the change from baseline in total Bath Ankylosing Spondylitis Functional Index (BASFI).	● Change from baseline in BASFI at Week 16
● To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the change from baseline in sacroiliac joint (SIJ) edema on MRI.	● Change from baseline in SIJ edema score on MRI at Week 16

[redacted]

Objectives	Endpoints
● To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the proportion of participants achieving an ASAS20 response.	● ASAS20 response rate at Week 16 ASAS20 response is defined as an improvement of ≥20% and an absolute improvement from baseline of ≥1 unit on a 10-point scale in at least three of the four main domains and no worsening of ≥20% and ≥1 unit at all in the remaining domain.
● To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the change from baseline in Short Form-36 Physical Component Summary (SF-36 PCS).	● Change from baseline in SF-36 PCS at Week 16
● To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) scores.	● Change from baseline in ASQoL score at Week 16
● To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the proportion of participants achieving ASAS partial remission.	● ASAS partial remission rate at Week 16 ASAS partial remission is defined as a value not above 2 units in each of the four main ASAS domains on a 10-point scale.
● To evaluate overall safety and tolerability of secukinumab.	● Number of participants with adverse events (AE) serious adverse events (SAE), clinically significant changes in laboratory value and vital signs.

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2.1 Primary estimands

The clinical question of interest is: What is the effect of secukinumab 150 mg s.c. versus placebo on the composite endpoint ASAS40 response at Week 16 and the completion of 16 week-treatment in Chinese participants with active nr-axSpA who are TNF-α naïve?

The justification for targeting this treatment effect is that we wish to estimate the effect of the study drug for the full duration when administered without dose changes.

The primary estimand is described by the following attributes:

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

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

[redacted]

C. Intercurrent event: the intercurrent event of discontinuation from treatment or study prior to Week 16 has been addressed via the variable definition

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

2.2 Secondary estimands

The clinical questions of interest are:

- What is the effect of secukinumab 150 mg s.c. versus placebo on the composite endpoint ASAS 40 response at Week 16 and the completion of 16 weeks-treatment in Chinese participants with active nr-axSpA?
- What is the effect of secukinumab 150 mg s.c. versus placebo on the composite endpoint ASAS 5/6 response at Week 16 and the completion of 16 weeks-treatment in Chinese participants with active nr-axSpA?
- What is the effect of secukinumab 150 mg s.c. versus placebo on the change from baseline in BASDAI at Week 16 in Chinese participants with active nr-axSpA had patients completed 16 weeks-treatment?
- What is the effect of secukinumab 150 mg s.c. versus placebo on the composite endpoint BASDAI 50 response at Week 16 and the completion of 16 weeks-treatment in Chinese participants with active nr-axSpA?
- What is the effect of secukinumab 150 mg s.c. versus placebo on the change from baseline in hsCRP at Week 16 in Chinese participants with active nr-axSpA had participants completed 16 weeks-treatment
- What is the effect of secukinumab 150 mg s.c. versus placebo on the change from baseline in BASFI at Week 16 in Chinese participants with active nr-axSpA had patients completed 16 weeks-treatment
- What is the effect of secukinumab 150 mg s.c. versus placebo on the change from baseline in SI joint edema on MRI at Week 16 in Chinese participants with active nr-axSpA had participants completed 16 week-treatment
- What is the effect of secukinumab 150 mg s.c. versus placebo on the composite endpoint ASAS20 response at Week 16 and the completion of 16 weeks-treatment in Chinese participants with active nr-axSpA?
- What is the effect of secukinumab 150 mg s.c. versus placebo on the change from baseline in SF-36 PCS at Week 16 in Chinese participants with active nr-axSpA had participants completed 16 weeks-treatment?
- What is the effect of secukinumab 150 mg s.c. versus placebo on the change from baseline in ASQoL at Week 16 in Chinese participants with active nr-axSpA had participants completed 16 weeks-treatment?
- What is the effect of secukinumab 150 mg s.c. versus placebo on the composite endpoint ASAS partial remission response at Week 16 and the completion of 16 weeks-treatment in Chinese participants with active nr-axSpA?

The justification for targeting this treatment effect is that we wish to estimate the effect of the study drug for the full duration when administered without dose changes.

[redacted]

The estimand definition of all secondary objectives related to response (e.g., ASAS 5/6, etc.) will have the same attributes as that for the primary estimand, except for the variable of interest.

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

a. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted nr-axSpA population
b. Variable: change from baseline in the variable of interest
c. Intercurrent event: discontinuation Population-level summary: difference in variable means between secukinumab and from treatment or study prior to Week 16
d. Placebo groups

3 Study design

This is a randomized, double-blind, placebo-controlled study of secukinumab 150 mg s.c. to evaluate the safety, tolerability and efficacy in Chinese participants with active non-radiographic axial spondyloarthritis (nr-axSpA).

A screening period of up to 10 weeks before randomization will assess participant eligibility, followed by 16 weeks of double blind treatment period and 44 weeks open label period.

Approximately 134 participants will be randomized in a ratio of 1:1 to receive secukinumab 150 mg s.c. or placebo:

- Group 1: 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: placebo (1 mL) s.c. PFS at BSL, Weeks 1, 2 and 3, followed by administration every four weeks starting at Week 4

Participants 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: CRP+ and MRI+, CRP+ and MRI-, CRP- and MRI+).

Additionally, it is planned to enroll no more than approximately 10% Tumor Necrosis Factor - Inadequate Response (TNFα-IR) participants in the study.

The primary analysis will be performed after all participants complete Week 16 visit to support registration in China.

From Week 16, all participants will switch to open label secukinumab 150 mg s.c., including all placebo participants. The first dose of open label secukinumab 150 mg s.c. should start at the Week 16 visit, only after performing all assessments for that visit. However, all participants and investigators/site staff will remain blinded to the original randomized treatment group assignment (150 mg vs placebo).

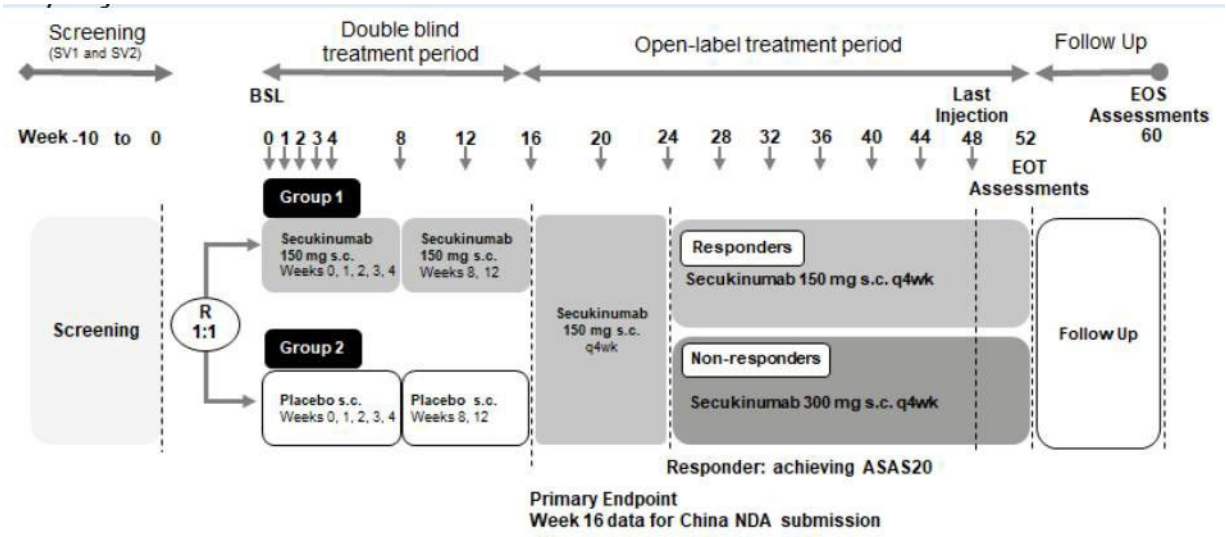
At week 24, non-responders (defined as not achieving ASAS20) will be escalated to secukinumab 300 mg s.c. Responders will continue secukinumab 150 mg s.c. treatment.

Study treatment will continue up to Week 48.

[redacted]

An end of treatment visit will be performed 4 weeks after last study treatment administration i.e. at Week 52 and a post treatment follow-up visit is to be done 12 weeks after last study treatment administration for all participants (regardless of whether they complete the entire study as planned or exit the study early).

Figure 3-1 Study Design



SV1: Screening Visit 1, SV2: Screening Visit 2, BSL: Baseline, EOT: End of Treatment, EOS: End of Study, R: Randomization, q4wk: every 4 weeks, s.c.: subcutaneously, ASAS: Assessment of SpondyloArthritis international Society, NDA: New Drug Application

4 Rationale

4.1 Rationale for study design

The randomized, double-blind, placebo controlled design used in this study is aligned with global phase III pivotal study (PREVENT) to show similar efficacy trend in Chinese population with active nr-axSpA. The study design is in compliance with the EMA/EMEA (European Medicines Agency) guidelines for AS (EMA 2009) and The National Medical Products Administration (NMPA) requirement in use of biologics drug, considered relevant for trials in nr-axSpA and available precedent. The treatment duration of placebo group in this study was kept for 16 weeks and participants in the two groups will receive 150 mg secukinumab s.c. open label treatment at Week 16 (cut-off point for primary analysis). The blinding to original treatment assignment is maintained to ensure reliable efficacy and safety measures over time. Participants who do not achieve ASAS 20 response at Week 24 visit will be escalated to 300 mg secukinuimab s.c. through Week 48 to assess if secukinumab 300 mg will provide further benefit to participants. The 300 mg dose is an approved dose for secukinumab in psoriasis, psoriatic arthritis, as well as in AS in regions globally. The regular assessments of disease activity ensure that participants who experience worsening of the disease in any of the treatment groups can exit the study upon their own wish or based on the advice of the investigator at any time.

4.1.1 Rationale for choice of background therapy

According to the guideline from international associations for treating axial spondyloarthritis, NSAIDs are considered as first-line therapy up to the maximum dose, taking risks and benefits into account, in both AS and nr-axSpA. Although sulfasalazine may be considered in patients with peripheral arthritis, conventional synthetic (cs) DMARDs including methotrexate (MTX) do not demonstrate credible evidence on efficacy in axSpA. Despite not being recommended by the international guidelines, csDMARDs are still regularly prescribed in China to treat nr-axSpA patients, given there are no biologic treatment approved. Short-term glucocorticoids treatment is also an option for cases refractory to NSAIDs.

In this study, participants are permitted to concomitantly use NSAIDs, csDMARDs and systemic glucocorticoids with specific restrictions detailed in Section 6.2.1. Starting from Week 24, the modification of the background therapy will be allowed for all participants as per the investigator's judgement or participant's need.

4.2 Rationale for dose/regimen and duration of treatment

In the previous AS pivotal studies CAIN457F2305 with intravenous loading, CAIN457F2310 with s.c. loading, CAIN457F2308 with s.c. loading and nr-axSpA pivotal study (CAIN457H2315 with or without s.c. loading), secukinumab 150 mg s.c. is a sufficient dose to provide consistent efficacy across multiple endpoints, with clinically meaningful improvements in axSpA measures of signs and symptoms, objective measures of inflammation, physical function, and patient-reported quality of life.

In contrast, 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-TNFα treatments as AS patients (Callhoff et al 2015). There was no evidence that different axSpA populations (e.g. AS and nr-axSpA) could require different dose regimens (Callhoff et al 2015), (Landewé 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 which is consistent with the dose regimen used in AS registration study CAIN457F2308 in China.

Notably, 300 mg s.c. administered monthly is an approved dose for secukinumab in psoriasis in China, and in Psoriatic arthritis (PsA) and AS globally. 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), (Mease et al 2015). The higher dose of secukinumab confers an additional benefit in other disease conditions (e.g., psoriasis, PsA and AS). This study will explore whether a higher dose of secukinumab will have an effect on participants with nr-axSpA with respect to increase in treatment response. The dose escalation will be starting at Week 24 in participants who do not achieve an ASAS20 response.

[redacted]

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

A placebo group up to the primary endpoint Week 16 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 group is necessary to obtain reliable efficacy measurements and can be supported from an ethical standpoint, as participants can continue on a range of concomitant treatments. Moreover, the inclusion of a placebo group is in accordance with previously implemented methodology including placebo setting in China centric AS study CAIN457F2308 (MEASURE 5) and in compliance with the EMA/EMEA guidelines for AS (EMA 2009), considered relevant for trials in nr-axSpA.

4.4 Purpose and timing of primary analyses/design adaptations

The primary analysis will be performed after all participants complete the Week 16 visit assessments to support regulatory submission in China. The final analysis will be conducted after all participants complete the study at Week 60 or end of study (EOS) visit.

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

Although unblinding will occur after the Week 16 database lock, the original randomization to active treatment vs. placebo will remain blinded to all investigators, site personnel, participants and sponsor's monitors until all participants have completed the study and the Week 60 database lock has occurred.

4.5 Risks and benefits

The risk to participants 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 25-June-2020, over 26,000 participants have been enrolled in both completed and ongoing studies with secukinumab, with over 22,000 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, rheumatoid arthritis, AS, PsA, multiple sclerosis and uveitis).

The risk profile of secukinumab in nr-axSpA is informed by the safety experience from trials performed in psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis.

Observed risks in global studies at doses up to 300 mg s.c. every 4 weeks from included infections, of which the most frequently reported were upper respiratory tract infections. Oral herpes, oral candidiasis and tinea pedis were also more frequently reported. Most of the infections were non-serious, mild to moderate in severity, clinically manageable and did not lead to treatment discontinuation. Neutropenia and hypersensitivity reactions are also risks observed with secukinumab. Cases of neutropenia were uncommon, generally mild to moderate, transient, did not lead to treatment discontinuation, and very few cases were temporally associated with non-serious infections.

[redacted]

In global phase III AS studies CAIN457F2305 and CAIN457F2310, secukinumab i.v. 10mg/kg, 75mg s.c. and 150mg s.c. were assessed in the study, data observed from 590 participants including participants enrolled from Taiwan demonstrated secukinumab provided significant improvement of signs and symptoms as well as quality of life for patients with active AS, 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. A China centric pivotal study CAIN457F2308 also demonstrated good efficacy of secukinumab 150mg s.c. in Chinese population with active AS, and the safety results studied in CAIN457F2308 in Chinese population wassimilar to overall population and comparable to global AS studies.

In a global phase III nr-axSpA pivotal study CAIN457H2315, secukinumab 150mg s.c. demonstrated efficacy versus placebo in terms of improvement of signs and symptoms of their disease was proved to be effcacious and significantly improved patient's outcome regarding of both patient reported outcomes (PROs) and objective measurements compared to placebo. The safety profile of secukinumab at both doses showed no new or unexpected safety signals and was consistent with the overall safety profile of secukinumab, based on the extensive safety data across multiple indications.

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

From the standpoint of the overall risk benefit assessment, the current trial with secukinumab in Chinese active nr-axSpA population is justified.

5 Study Population

The study population will consist of male and female participants (≥ 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.

Participants must have active disease despite current or previous NSAID, non-biologic DMARD, and/or anti-TNFα therapy. Participants 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. Participants 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 participants that are TNFα-IR to no more than 10% of the overall randomized population. Due to the long wash out required for some TNFα-IR participants, enrolment of TNFα-IR participants will end two months prior to the projected end of screening period.

The study aims to randomize approximately 134 analyzable participants in total. Enrollment will stop as soon as the target number of randomized analyzable participants is reached.

[redacted]

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

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study.
2. Male or non-pregnant, non-lactating female participant at least 18 years of age.
3. Diagnosis of axSpA according to ASAS axSpA criteria:
   a. Inflammatory back pain for at least 6 months
   b. Onset before 45 years of age
   c. Sacroiliitis on MRI (as assessed by central reader) with ≥ 1 SpA feature OR Human Leukocyte Antigen-B27 (HLA-B27) positive with ≥2 SpA features
4. Objective signs of inflammation at screening, evident by either
   - MRI with Sacroiliac Joint inflammation (as assessed by central reader)

   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. Participants 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. Participants 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. Participants 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 (detailed in Section 6.2.1 and Section 6.2.2)
11. Participants who have previously been on a TNFα inhibitor will be allowed entry into study after an appropriate wash-out period prior to randomization: (detailed in Section 6.2.1 and Section 6.2.2)
    - 4 weeks for Enbrel® (etanercept) or "Yi Sai Pu", "An Bai Nuo" and "Qiang Ke" – 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

[redacted]

- 10 weeks for Cimzia® (certolizumab) – with a terminal half-life of 14 days

12. Participants 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 (detailed in Section 6.2.1 and Section 6.2.2)
13. Participants on MTX must be on stable folic acid supplementation before randomization (detailed in Section 6.2.1 and Section 6.2.2)
14. Participants 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 (detailed in Section 6.2.1 and Section 6.2.2)
15. Participants taking systemic corticosteroids have to be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization (detailed in Section 6.2.1 and Section 6.2.2).

5.2 Exclusion criteria

Participants meeting 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 participants.

1. Participants 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
2. Inability or unwillingness to undergo MRI scan (e.g., participants 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 computed tomography (CT) scan with evidence of ongoing infectious or malignant process, obtained within 3 months of screening and evaluated by a qualified physician
4. Participants 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. Participants previously treated with any biological immunomodulating agents, except those targeting TNFα
11. Participants who have taken more than one anti-TNFα agent

[redacted]

12. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g., anti-CD52, 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 Effective contraception methods include:
    - Total abstinence, when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least 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 participants on the study, the vasectomized male partner should be the sole partner for that participant
    - 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 or placement of an intrauterine device (IUD) or intrauterine system (IUS)

    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), total 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 childbearing potential.

    If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the inform consent form (ICF).
15. Active ongoing inflammatory diseases other than nr-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 participant and/or places the participant at unacceptable risk for participation in an immunomodulatory therapy

[redacted]

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 Serum Glutamic Oxaloacetic Transaminase (SGOT) (Aspartate Aminotransferase (AST)), SGPT (Alanine Aminotransferase (ALT)), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria:
    - Any single parameter may not exceed 2 x 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 participants with one kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6 µmol/L)
20. Screening total White blood cell(s) (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 8-1. Participants with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the participant 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 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 participant 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 subcutaneous 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

[redacted]

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

6 Treatment

6.1 Study treatment

Novartis Global Clinical Supply 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

At Week 16, all participants will switch to open label secukinumab 150 mg, including all placebo participants; however, all participants, investigators and site staff will remain blinded to the original randomized treatment group assignment (150 mg vs placebo) until the end of the trial.

At Week 24, non-responders (defined as not achieving ASAS20) will be escalated to secukinumab 300 mg (two PFS for 150 mg dose). Responders will continue secukinumab 150 mg treatment.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	**Pharmaceutical Dosage Form**	**Route of Administration**	**Supply Type**	**Sponsor (global or local)**
Secukinumab 150 mg	PFS	subcutaneous injection	Double Blind Supply	Sponsor (global)
Secukinumab 150 mg	PFS	subcutaneous injection	Open label	Sponsor (global)
Secukinumab placebo	PFS	subcutaneous injection	Double Blind Supply	Sponsor (global)

In the double blind period, the Secukinumab/Placebo PFSs are packaged in a double-blinded fashion to meet dosing requirements until including Week 12 dispensing, thereafter at Week 16 and onwards open label treatment will start.

In the open label period (starting at Week 16), the study medication will be provided in open label fashion for the 150 mg and from Week 24 onwards for the 300 mg doses. Open label medications will be supplied until the last dose is given at Week 48.

The double blind period medication will be labeled as follows:

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

The open label period study medication will be labeled as follows:

- Open label Secukinumab PFS will be labeled as AIN457 150mg/1mL

[redacted]

For detailed instructions on storage of the investigational treatments, please refer to medication label.

6.1.2 Additional study treatments

Not Applicable

6.1.3 Treatment arms/group

Double Blind Period (Treatment Period 1)

Participants in double-blind period will be assigned to one of the following two treatment groups in a ratio of 1:1. Participants will receive study treatment at BSL, Weeks 1, 2, 3, and 4, followed by treatment every 4 weeks through Week 12.

- Group 1: secukinumab 150 mg (1 mL, 150 mg/mL) s.c. PFS at BSL, Weeks 1, 2, and 3, followed by administration every 4 weeks starting at Week 4.
- Group 2: placebo (1 mL) s.c. PFS at BSL, Weeks 1, 2 and 3, followed by administration every 4 weeks starting at Week 4.

Open Label Period (Treatment Period 2 and 3)

Treatment Period 2: At Week 16, Group 1 participants will continue using secukinumab 150 mg and Group 2 participants will start receiving secukinumab 150 mg dosing every four weeks. Treatment will be provided open label from Week 16 onward, as all participants will be taking 150 mg s.c. every 4 weeks. However, all participants and investigators/site staff will remain blinded to the original randomized treatment group assignment (150 mg vs placebo).

Treatment Period 3: At Week 24, participants in open label period will be assessed as being Open Label Period Responder or Open Label Period non-responder and will receive the study treatment every 4 weeks through Week 48 as follows.

- Open Label Period **Responder**: Secukinumab 150 mg provided in a 1 mL PFS (**one** PFS for 150 mg dose, s.c.), administration every 4 weeks starting at Week 24.
- Open Label Period **non-responder**: Secukinumab 150 mg provided in a 1 mL PFS (**two** PFS for 300 mg dose, s.c.), administration every 4 weeks starting at Week 24.

6.1.4 Treatment duration

The planned study duration is 60 weeks with the last secukinumab treatment administration at Week 48. Participants may be discontinued from treatment earlier due to unacceptable toxicity, disease progression and/or if the treatment is discontinued at the discretion of the investigator or the participant. For participants who in the opinion of the investigator are still deriving clinical benefit from the study drug, every effort will be made to continue provision of study treatment.

Participants should continue to receive the study treatment until one or more criteria for treatment discontinuation described in Section 9.1.1 are met.

[redacted]

6.2 Other treatments

6.2.1 Concomitant therapy

During this study, NSAIDs, selected analgesics, selected disease-modifying anti-rheumatic drugs (DMARDs), i.e. MTX and sulfasalazine, and systemic corticosteroids are permitted as part of participants' routine medical care and will not be provided by Novartis. The investigational site and / or the participant's treating physician are responsible for prescribing and providing any background therapy.

The investigator should instruct the participant to notify the study site about any new medications he/she takes after the participant was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded in the Prior/Concomitant medications electronical case report form (eCRF) page.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Guidelines for the use of specific medications are provided below:

Methotrexate

Participants taking MTX (≤ 25 mg/week) must be on a stable dose for at least 4 weeks before randomization and maintained stable until Week 24. Any changes in dose or initiation after Week 24 must be recorded in the Prior/Concomitant medications eCRF page.

Folic acid

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

Sulfasalazine

Participants taking sulfasalazine (≤ 3 g/day) must be on a stable dose for at least 4 weeks before randomization and maintained stable until Week 24. Any changes in dose or initiation after Week 24 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 three times a day (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 participants who require a drug elimination procedure. If a participant 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 24 assessments are completed, leflunomide therapy may be initiated as a background medication. Any initiation or changes in dose after Week 24 must be recorded in the Prior/Concomitant medications eCRF page.

Systemic corticosteroids

[redacted]

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 24, the dose and regimen of systemic corticosteroids may be modified as per investigator's judgment and participant's needs, 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 24. 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.

Any change in the dose of systemic corticosteroids, or any corticosteroid injections during the trial must be recorded in the Prior/Concomitant medications on the corresponding eCRF page.

NSAIDs including COX-1 or COX-2 inhibitors and acetaminophen/paracetamol

Participants on regular use of non-steriodal anti-inflammatory drugs (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 (Pro re nata) can be taken during the study; however, participants should refrain from any intake during at least the 24 hours before a visit with disease activity assessment.

After the Week 24 assessments are completed, a change in the NSAID intake regimen is permitted. [redacted]

TNFα inhibitors

If TNFα inhibitors are chosen as escape treatment for participants considered as inadequate responders from Week 28, a wash out period has to be considered after administration of the last dose of study treatment for safety reasons. 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 be considered standard of care and will not be supplied by the sponsor.

6.2.2 Prohibited medication

Use of the treatments displayed in Table 6-2 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 during the study period or 6 weeks prior to randomization and until 12 weeks after last study treatment administration (follow up visit).

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
Etanercept or "Yi Sai Pu", "An Bai Nuo" and "Qiang Ke"	4 weeks washout period prior to randomization to until Week 28	Delay randomization or discontinue from study treatment

[redacted]

Medication	Prohibition period	Action taken
Infliximab	8 weeks washout period prior to randomization to until Week 28	Delay randomization or discontinue from study treatment
Adalimumab, golimumab, certolizumab	10 weeks washout period prior to randomization to until Week 28	Delay randomization or discontinue from study treatment
Unstable dose of MTX or sulfasalazine	4 weeks prior to randomization to until Week 24	Achieve stable dose for at least 4 weeks prior to randomization and remain on a stable dose up to Week 24
Other DMARD (except MTX or sulfasalazine)	4 weeks washout period prior to randomization to until Week 24,	Delay randomization or discontinue from study treatment
Leflunomide	8 weeks washout period prior to randomization to until Week 24	Delay randomization or discontinue from study treatment
Leflunomide with Cholestyramine washout	4 weeks washout period prior to randomization to until Week 24	Delay randomization or discontinue from study treatment
Unstable dose of NSAIDs (COX1 or COX2 inhibitors)	2 weeks prior to randomization to until Week 24	Achieve stable dose for at least 2 weeks prior to randomization and remain on a stable dose up to Week 24
Systemic corticosteroids > 10 mg prednisone equivalent*	2 weeks prior to randomization to until Week 24	Achieve stable dose for at least 2 weeks prior to randomization and remain on a stable dose up to Week 24
Intra-articular steroid injections	4 weeks prior to randomization to until Week 24	Delay randomization or discontinue from study treatment
Any biological immunomodulating agents, except those targeting TNFα**	From screening to follow up visit	No prior exposure allowed
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g., anti-CD52, anti-CD4, anti-CD5, anti-CD3, anti-CD19)	From screening to follow up visit	No prior exposure allowed
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer) prior to randomization to follow up visit	Delay randomization or discontinue from study treatment
Analgesics other than paracetamol/acetaminophen or low strength opioids PRN(Pro re nata)	4 weeks prior to randomization to follow up visit	Delay randomization or discontinue from study treatment
Live vaccinations	6 weeks prior to randomization to follow up visit	Delay randomization or discontinue from study treatment
Traditional Chinese Medicines***	Until Week 24, if adjustment needed by investigator's judgement	Delay randomization or discontinue from study treatment

*See details about corticosteroid management in Section 6.2.1.
**These agents fall under the category of biologic immunomodulators and are prohibited medications. Administration of these agents requires study treatment discontinuation (see Section 9.1)
***Traditional Chinese herb medicines, Chinese patent medicines etc.

6.2.3 Escape Medication

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

[redacted]

From Week 28 on, based on the clinical judgment of disease activity by the investigator and the participant, participants may be considered as inadequate responders. Participants 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", participants can be switched to treatment according to locally applicable clinical practice.

Participants have the option to either discontinue study treatment (escape to locally applicable clinical practice treatment but continue study participation) or completely discontinue from the study (no further study participation) for any reason.

While all participants have already switched to open label treatment with secukinumab 150 mg at Week 16, the originally randomized treatment assignment before Week 16 (secukinumab 150 mg or placebo) will remain blinded until the end of study. From Week 24 onward, if based on the clinical practice, the participants escape to include the use of a biologic such as a TNFα inhibitor, it should be prescribed in accordance with investigator practice and local treatment guidelines. Participants switching to a biologic therapy (e.g. anti-TNFα) other than secukinumab must not receive any further study medication and the investigator will be recommended to consider a wash out period after the last administration of study treatment prior to starting any other biologic treatment. All other participants will continue their original assigned treatment.

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

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

Participants numbers are assigned when the site creates the first entry for the participant in the CRF, therefore CRF entry must be created prior to contacting the Interactive Response Technology system.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.3.2 Treatment assignment, randomization

At baseline visit, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment groups. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the

[redacted]

participant to a treatment group and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment groups, which in turn are linked to medication numbers. A separate medication list will be produced by Novartis Global Clinical Supply using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Only at Week 24, the participant's responder status (responder / non-responder), which will be based on ASAS20 criteria, must be entered into IRT. Participants considered to be responders will continue to receive secukinumab 150 mg up to Week 48, unless they have discontinued study treatment. Participants considered to be non-responders will receive secukinumab 300 mg up to Week 48, unless they have discontinued study treatment.

Randomization will be stratified by according to the subgroup of objective signs of inflammation they belong to (based on their CRP and MRI status at screening).

- CRP+ and MRI+
- CRP+ and MRI-
- CRP- and MRI+

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

6.4 Treatment blinding

This is a double-blind randomized treatment trial. Unblinding will occur after the Week 16 database lock to support regulatory submission. However, the participants, investigators, site personnel, persons performing the assessments and sponsor's monitor will remain blinded to original treatment assignment from the time of randomization until the final database lock and analyses are completed, 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 16 will be concealed up to the final datalock and until analyses are completed. Moreover the study treatments in the form of PFS for s.c. injection, filled with secukinumab or placebo are identical in appearance during the double-blind treatment period.

[redacted]

The hsCRP results from samples collected during the treatment period will be revealed only after the database lock and analyses are completed.

[redacted]

For details regarding the planned primary endpoint analysis, refer to Section 12.7.

The reading of MRI scan 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 after completion of the study.

Unblinding of original randomized treatment assignment (at the site level and below) before the final database lock and analyses are completed will only occur in the case of participant emergencies.

Unblinding of the sponsor staff (except field monitor) will occur at the time of the primary endpoint analysis. The study will be conducted in an open label fashion after Week 16, however, original group assignment from the randomization will remain blinded until the end of study for site staf and field monitors.

Table 6-3 Blinding Level

	Time or Event			
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single participant unblinded)**	**Primary Endpoint Analysis**
Participants	B	B	B	B
Site staff	B	B	B	B
Field Monitor	B	B	B	B
Drug Supply and Randomization Office	UI	UI	UI	UI
Statistician/statistical programmer/data analysts	B	B	B	UI
All other sponsor staff not identified above	B	B	B	UI

B: Remains blinded UI: Allowed to be unblinded on individual participant level

6.5 Dose escalation and dose modification

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 participant is deemed to be placed at a significant safety risk unless dosing is temporarily interrupted. In such cases study treatment should be interrupted only during the time that this risk is present and ongoing. Study treatment can be restarted at the next scheduled visit after resolution of the safety risk.

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, the participant must discontinue the study treatment.

Any study treatment interruption must be recorded on the Dosage Administration Record eCRF.

In all cases the **original visit schedule should be maintained** (no recalculation from the last visit).

[redacted]

6.5.1 Dose escalation guidelines

Only at the Week 24 visit, any participant who does not meet ASAS20 criteria per IRT confirmation is categorized as non-responder to the secukinumab 150 mg q4wk dose and will be escalated to 300 mg q4wk in an open label fashion.

6.6 Additional treatment guidance

Treatment modifications as new therapeutic interventions or a significant change to ongoing therapy must not be made before completion of Week 24 assessments.

From Week 24 on, if the participant 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 6.2.1. All medication changes must be recorded in the Prior/Concomitant medications eCRF page.

Participants who do not achieve ASAS 20 response at Week 24 visit will be escalated to 300 mg secukinuimab s.c. through Week 48 to assess if secukinumab 300 mg will provide further benefit to participants.

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 participant inadequate responder or non-responder to study treatment.

Although no participant will be restricted from receiving necessary medications for lack of benefit or worsening of disease, if treatment with prohibited biologics (as described in Section 6.2.2) occurs, participants may remain in the trial but must discontinue study treatment. Efficacy will be assessed in detail at every study visit, and participants who are deemed not to be benefiting from the study treatment based on safety and efficacy assessments (see Section 9.1.1) 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 participant's clinical judgment after all Week 24 assessments are completed. Please see Section 6.2.1, Section 6.2.2 and Section 9.1.1 for details.

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

6.6.1 Treatment compliance

Every time the study treatment is to be administered, IRT needs to be accessed for the medication (kit) number. The date and time of all study treatment administered during the study and any deviations from the protocol treatment schedule will be captured by the investigator staff on the appropriate Dosage Administration Record eCRF page.

In this study, the compliance to the planned administration schedule is expected to be high since the study treatment will be administered on site by self-administration by the participants or the trained site staff.

[redacted]

Exposure to the study treatment will be based on the number of injections administered. Compliance with the study treatment will be assessed by the field monitor at each visit using information provided by the pharmacist or by the investigator. Compliance is expected to be 100%, unless temporary interruption is needed for safety reasons as described in Section 6.5.

6.6.2 Recommended treatment of adverse events

Medication used to treat AE must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the investigator to select the participant's next treatment regimen, and after discussion and agreement with the sponsor. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant 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 participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- site number
- participant number

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

After an emergency unblinding, study medication must be discontinued.

In the case of accidental unblinding, participants will not be replaced by newly enrolled participants.

6.7 Preparation and dispensation

Each study site will be supplied with study drug of identical appearance in packaging as described under investigational and control drugs section.

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

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

[redacted]

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

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

The PFS (150 mg active/placebo) sealed in their outer box must be stored in a access controlled/locked refrigerator between 2°C and 8°C (36°F and 46°F) (Do Not Freeze) and protected from light. They must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations.

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

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

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

[redacted]

The study drug will be administered at the investigational site in double-blind followed by open label fashion as described in Section 6.1.4.

For each study visit at the site, all study assessments including completion of PROs should be completed prior to the administration of the study treatment.

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

[redacted]

All doses of study treatment (secukinumab and placebo) will be administered at the study site, and it is preferred that participants self-administer. However, if the participant is not able or not willing to self-administer, administration will be performed by study site staff. The injections will be self-administered by the participant at the study site under the supervision of a site staff member after the study assessments for the visit have been completed. Participants will be instructed by the site staff on how to self-inject study treatment using a PFS, following the Instructions for Use (IFU). Home administration is not allowed in this study except when there is global health disruptive event, such as pandemic/epidemic (e.g. COVID-19). The instructions and procedures are outlined in Section 16.9.

Any PFS for which a defect or malfunction is noticed prior to or during the administration at any of the study visits, must be kept at the site until guidance is received from Novartis on whether it should be returned to Novartis for investigation or discarded. PFS identified as defective should be stored according to local guidelines, until specific instruction is discussed with Novartis personnel. Additionally, from BSL onwards, any noticed defect, malfunction, problem during the injections or product complaints with the PFS should be recorded in the source document. Sites should detail the issue, the date, the kit number and the visit number. Site will be asked to record based on their judgment whether the observed issue was primarily related to the PFS device or to the user. PFS malfunctions should also be immediately reported to Novartis personnel as a necessary replacement kit may need to be provided.

Prior to administration the boxes containing the PFSs with study treatment, it should be allowed to come to room temperature **unopened** for 15-30 minutes prior to injection.

The injections will be administered into the appropriate site of the body (thighs, arms, abdomen), and each injection should be given at a different injection site to reduce the risk of reaction. Each new injection should be given at least one inch from the previously used site.

Used safety syringes should be disposed immediately after use in a sharps container or according to the local regulatory requirements.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

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

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

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

[redacted]

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

The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
  - As applicable, Pregnancy Outcomes Reporting Consent for female participants who took study treatment

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

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

When there is global health disruptive event, such as pandemic/epidemic (e.g. COVID-19) that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the instructions and procedures of this situation are outlined in Section 16.9.

8 Visit schedule and assessments

The Assessment Schedule Table 8-1 lists all of the assessments and when they are performed.

Participants should be seen for all visits/assessments as outlined in the assessment schedule Table 8-1 or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who prematurely discontinue study should return for end of treatment visit 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.

At a minimum, participants will be contacted for safety evaluations during the 30 days following the last study visit, however preferably for a follow-up visit 12 weeks after last study treatment. Attempts to contact the participant should be recorded in the source documentation.

If a global health disruptive event, such as a pandemic/epidemic (e.g. COVID-19) limits or prevents on-site study visits, study treatment dispensing and other study assessments may be impacted. The instructions and procedures of this situation are outlined in Section 16.9.

[redacted]

Table 8-1 Assessment Schedule

Period	Screening[1]		Treatment Period 1							Treatment Period 2		Treatment Period 3								Follow Up	Unscheduled Visit
Visit Name	SV 1	SV 2	BSL	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	EOT[2]	Follow Up[2]	
Weeks	-10 to -4	-4 to 0	0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52	60	Unscheduled
Informed consent	X																				
Inclusion / Exclusion criteria[3]	X	X	X																		
Medical history/current medical conditions[3]	X	X	X																		
Prior medication and Significant non-drug therapies	X	X	X																		
nr-axSpA assessment and history of extra-axial involvement[4]	X																				
Demography	X																				
MRI [redacted]	X[5]									X									X		
X-Ray of sacroiliac joints	X[6]																				
Cardiovascular medical history			X																		
Smoking history			X																		
Physical Examination (full)			S							S									S		
Physical Examination (abbreviated)		S		S	S	S	S	S	S		S	S	S	S	S	S	S	S			
Height		X																			
Weight		X	X							X									X	X	

[redacted]

Period	Screening[1]		Treatment Period 1							Treatment Period 2		Treatment Period 3								Follow Up	Unscheduled Visit
Visit Name	SV 1	SV 2	BSL	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	EOT[2]	Follow Up[2]	
Weeks	-10 to -4	-4 to 0	0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52	60	Unscheduled
Electrocardiogram (ECG)			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 or QuantiFERON TB-Gold test[7]		X																			
Chest X-ray or CT[8]		S																			
Hematology, Blood Chemistry, Urinalysis		X	X	X	X		X		X	X		X	X			X			X	X	
Pregnancy Test (serum)		X																			
Urine / Serum Pregnancy Test			S				S			S		S		S		S			S	S	
Hepatitis B, C or HIV serology[9]		S																			
Randomization via IRT			X																		
[redacted]																					
Responder assessment via IRT												X									
On-site administration of S.C. study treatment by PFS[10]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Concomitant medication / non-drug therapy	X	Update as necessary																			X
Adverse events/SAEs (including injection site reactions)[11]	X	Update as necessary																			X
[redacted]																					

[redacted]

Period	Screening[1]		Treatment Period 1							Treatment Period 2		Treatment Period 3								Follow Up	Unscheduled Visit
Visit Name	SV 1	SV 2	BSL	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	EOT[2]	Follow Up[2]	
Weeks	-10 to -4	-4 to 0	0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52	60	Unscheduled
Patient's global assessment of disease activity (VAS)																					
Patient's assessment of back pain intensity (VAS)																					
BASFI																					
BASDAI																					
ASQoL																					
SF-36 v2																					
High sensitivity C-Reactive protein (hsCRP)																					
HLA-B27		X																			
Lipids[12]			X					X		X									X		

[redacted]

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] If the participant's washout period ≤ 4 weeks, Screening visit 1 (SV1) and Screening visit 2 (SV2) can be performed on the same day.
[2] For all participants who discontinue the study prematurely, the investigator should ensure that the participant completes an end of treatment visit 4 weeks after last study treatment and also returns after an additional 8 weeks for a final follow-up visit (12 weeks after last study treatment).
[3] 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.
[4] Extra-axial involvement such as uveitis, psoriasis, inflammatory bowel disease, dactylitis, enthesitis, peripheral arthritis
[5] Unless MRI according to the imaging criteria was taken within the past 3 months prior to targeted Baseline. A copy of MRI or radiologist's report must be kept in the source documentation.
[6] Unless X-ray according to the imaging criteria was taken within the past 3 months prior Screening. A copy of the x-ray or radiologist's report must be kept in the source documentation
[7] 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.
[8] A chest X-ray or CT 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 participant meets inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation. The X-ray may be replaced by a CT assessment. A copy of the x-ray/ CT or radiologist's report must be kept in the source documentation.
[9] 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.
[10] All the assessments need to be completed before the administration.
[11] AEs/SAEs occurring after the participant has signed the informed consent must be captured on the appropriate eCRF page.
[12] Sample must be obtained fasting

[redacted]

8.1 Screening

Re-screening of a participant who has failed screening may be allowed. In such cases, a new ICF must be signed. A new participant number will be assigned to the participant. The re-screen form will have to be completed in the eCRF and in IRT to provide the original participant number. An individual participant can only be re-screened once for the study.

All required screening assessments must be repeated if they do not meet the allowed time window for screening when the participant is re-screened for participation in the study.

Once the number of participants screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the participants who screen failed will not be permitted to re-screen.

The study IRB/IEC approved informed consent form must be signed and dated before any screening procedures are performed, except for radiological evaluations which were performed as part of the participant's clinical standard of care within the acceptable screening window.

Participants will be evaluated against study inclusion and exclusion criteria and safety assessments (refer to Table 8-1). Screening assessments must be repeated if performed outside of the specified screening window (refer to Table 8-1). Participants must meet all inclusion and none of the exclusion criteria at screening in order to be eligible for the study.

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 participant 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 8-1.

Screening will consist of two consecutive visits. During Screening visit 1, initial assessments will be performed as outlined in Table 8-1. 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 participant 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 participants evaluated at Screening visits 1 and 2 for eligibility should not be screen failed on the basis of a medication requiring washout, unless the participant will be unable to complete the washout in the appropriate time frame before randomization.

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.

[redacted]

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form may discontinue from the study prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form.

The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE section for reporting details). Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. If the participant fails to be randomized in the double-blind treatment period at baseline, the IRT must be notified within 2 days of the screen fail that the participant was not randomized and the reason for not being randomized will be entered on the Screening Phase Disposition eCRF page.

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

8.2 Participant demographics/other baseline characteristics

Country-specific (China) regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF.

Participant demographic and baseline characteristic data to be collected on all participants include:

- Age, sex, race and ethnicity
- Relevant nr-axSpA and general medical history/current medical condition present before inform consent was signed, 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.

Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities

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

8.3 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)

8.3.1 Assessment of SpondyloArthritis International Society criteria (ASAS)

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

Main ASAS domains:

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

Additional assessment domains:

2. C-reactive protein (acute phase reactant)

8.3.1.1 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.

8.3.1.2 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.

8.3.1.3 ASAS 5/6 improvement criteria

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

8.3.1.4 ASAS partial remission criteria

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

8.3.2 Patients 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?*"

8.3.3 Patients assessment of back pain intensity (VAS)

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

8.3.4 Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those participants with AS. The ten questions were chosen with major input from participants 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.

8.3.5 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 participants 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.

8.3.5.1 BASDAI 50

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

[redacted]

[redacted]

8.3.8 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]

[redacted]

8.3.12 MRI

Magnetic resonance imaging (MRI) scans will be performed as defined in the schedule of assessments Table 8-1 and according to the imaging acquisition guidelines provided by the central imaging lab. The MRI protocol for each participant will include scans of the spine (cervical, thoracic and lumbar) and pelvis, including both sacroiliac joints. The MRI scans should be transferred as de-identified electronic files to the central imaging lab following acquisition within the time window specified in the imaging manual. The central imaging lab will conduct independent review for all spine and sacroiliac MR imaging in this trial.

[redacted]

When there is global health disruptive event, such as pandemic/epidemic (e.g. COVID-19) that may limit or prevent on-site study visits to collect images, the instructions and procedures of this situation are outlined in Section 16.9.

8.3.13 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.

8.4 Safety and Tolerability

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed. If global health disruptive event, such as pandemic/epidemic (e.g. COVID-19) limits or prevents on-site study visits, the safety assessment may not be performed. The instructions and procedures of this situation are outlined in Section 16.9.

- QuantiFERON TB-Gold test or PPD skin test
- Chest X-ray or CT
- Physical examination
- Vital signs
- Height and weight
- Laboratory evaluations
- [redacted]
- Electrocardiogram
- Pregnancy and assessment of fertility
- Local tolerability (Injection site reactions)
- Tolerability of secukinumab

For details on AE collection and reporting, refer to AE Section 10.1.1.

Table 8-2 Safety and tolerability assessments

Assessment	Specification
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.
Vital signs	Vital signs will include blood pressure and pulse rate measurements after 5 minutes rest in sitting position. If possible, vital signs assessments should be performed by the same study site staff member using the same validated device throughout the study.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing) (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.

[redacted]

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected listed below (except urinalysis, urine/serum pregnancy test and erythrocyte sedimentation rate). Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual. For the identification of clinically notable values, see Section 16.1. All participants with laboratory tests containing clinically significant abnormal values are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

Table 8-3 Clinical Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells, Red Blood Cell, Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, white blood cell counts)
Chemistry	Albumin, Alkaline phosphatase, ALT(SGPT), AST (SGOT), Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Direct Bilirubin, Total Bilirubin, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Glucose (fasting)
Urinalysis	Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) The urinalysis results for standard parameters such as protein, glucose, blood and WBCs will be recorded in the appropriate eCRF page.
Lipid panel and marker	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.
Pregnancy Test	Serum / Urine pregnancy test

8.4.2 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as indicated in Table 8-1. In this study, ECG will be performed locally. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

Each ECG tracing should be labeled with the study number, participant number, and date. The original ECG tracing on non-heat-sensitive paper or its certified copy appropriately signed, must be collected and kept in the source document at the study site.

Although there is no exclusion criterion based on ECG results, the baseline ECG at the Randomization visit must be reviewed locally for major abnormalities before administration of study treatment.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

8.4.3 Pregnancy

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 in central lab, the rest pregnancy

[redacted]

assessments as indicated in Table 8-1 can be urine pregnancy test or serum pregnancy test as applicable in local lab. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative. If positive, the participant must be discontinued from the study treatment. Additional pregnancy testing might be performed if requested by local requirements.

8.4.4 Chest X-ray or CT

A chest X-ray or CT scan 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, TB.

When there is global health disruptive event, such as pandemic/epidemic (e.g. COVID-19) that may limit or prevent on-site study visits to collect images, the instructions and procedures of this situation are outlined in Section 16.9.

8.4.5 QuantiFERON TB-Gold test or PPD skin test

Either a QuantiFERON TB-Gold test or a PPD skin test must be performed at screening. Participants with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the participant has no evidence of active TB, or if presence of latent TB 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 participant's eligibility. The test will be used to screen the participant population for latent TB 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 participant'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 participants must return to the investigators' site within that time for a proper evaluation of the injection site. This will determine whether the participant 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.

[redacted]

[redacted]

8.4.7 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.

8.4.8 Tolerability of secukinumab

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

8.4.9 Appropriateness of safety measurements

The safety assessments selected are standard and adequate for this indication/participant population. 12-week period following the last administration of study treatment should be reported.

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

8.5 Additional assessments

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

[redacted]

8.5.1 Clinical Outcome Assessments (COAs)

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

- SF-36
- ASQoL

All questionnaires will be available, in the local languages.

All questionnaires will be completed at the scheduled study visit prior to the participant seeing the investigator for any other clinical assessment or evaluation. The participant 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 participant to complete any missing responses. Guidelines for administering the PRO questionnaires can be found in Section 16.8. 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 AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the participant. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 16.8 of the protocol. Investigators should not encourage the participants 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.

In the event of global health disruptive event, such as pandemic/epidemic (e.g. COVID-19) that limits or prevents on-site study visits, selected efficacy assessments including PPROs can alternatively be done as per the instructions and procedures of this situation outlined in Section 16.9.

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

The SF-36 is a widely used and extensively studied instrument to measure health-related quality of life among healthy participants 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 participants.

The purpose of the SF-36 in this study is to assess the health-related QoL of participants. 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 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

[redacted]

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.

8.5.1.2 Ankylosing Spondylitis Quality of Life (ASQoL)

The ASQoL is a self-administered questionnaire designed to assess health-related quality of life in adult pateints 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 participants in this study.

[redacted]

[redacted]

[redacted]

8.5.5 HLA-B27

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

8.5.6 X-ray of the sacroiliac joints

X-rays will be obtained at screening visit and according to the imaging acquisition guidelines provided by the central imaging lab. The X-ray requirements include 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.

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

When there is global health disruptive event, such as pandemic/epidemic (e.g. COVID-19) that may limit or prevent on-site study visits to collect images, the instructions and procedures of this situation are outlined in Section 16.9.

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

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

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

[redacted]

Study treatment must be discontinued under the following circumstances:

- Participant decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the participant
- Following emergency unblinding
- Emergence of the following adverse events:
  - 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
  - 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
  - Life-threatening infection
  - Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the participant at a safety risk for continuation in the study (A general guidance on clinically notable laboratory values is provided in Section 16.1.)
  - Use of any prohibited treatment as defined in Section 6.2.2
  - Any protocol deviation that results in a significant risk to the participant's safety
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study

In addition to these requirements for study treatment discontinuation, the investigator should discontinue study treatment for a given participant if on balance, he/she thinks that continuation would be detrimental to the participant's well-being.

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

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

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

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

[redacted]

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

Participants who discontinue study should undergo an end of treatment visit 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 60 (12 weeks after last study treatment; see Table 8-1).

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

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

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

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

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

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 participant are not allowed unless safety findings require communicating or follow-up.

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

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 Lost to follow-up

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

[redacted]

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Practical reasons (including slow enrollment), or for regulatory or medical reasons
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. 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 participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion or end of study (i.e Week 60) visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

Continuing care should be provided by the investigator and/or referring physician based on participant availability for follow-up. This care may include:

- Enrollment in a rollover extension program or equivalent program, as applicable, provided the participant completed end of study visit (i.e Week 60) and could still deriving benefit from the study treatment based on investigator's decision.

A participant will be considered to have completed the double blind period if he/she received a maximum of 16 weeks of study treatment and upon completion of the scheduled study assessments and procedures up to and including Follow Up visit (i.e. Week 60) or continuation into the open label period.

A participant will be considered to have completed the open label period if he/she has received a maximum of 48 weeks of study treatment and has completed the scheduled study assessments and procedures up to and including Follow Up visit (i.e. Week 60).

Information on the participant's completion or discontinuation of the study and the reason for discontinuation of the study will be recorded on the study disposition eCRF page.

In any case, the investigator or site staff must contact the IRT as soon as possible to record the participant's study completion and/or discontinuation.

The investigator must provide follow-up medical care for all participants 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.

[redacted]

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

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

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

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments. Patient-Reported Outcomes are considered as other assessments to detect adverse events, see Section 8.5.1.

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

1. The severity grade include the following:
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved or recovering/resolving must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

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

- Dose not changed
- Dose Reduced/increased

[redacted]

- Drug interrupted/withdrawn

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

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

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

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

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

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the form of IN. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed.

The investigator should also instruct each participant to report any new adverse event (beyond the protocol observation period) that the participant, or the participant'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.

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1.

10.1.2 Serious adverse events

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

- fatal
- life-threatening

[redacted]

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

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

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

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

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

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

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 12 weeks following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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

[redacted]

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with European Union (EU) Guidance 2011/C 172/01 or as per China national regulatory requirements.

10.1.4 Pregnancy reporting

Pregnancies

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.

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported. Information will be collected at three time points after the estimated date of delivery and for a period of 12 months.

Follow up of the pregnancy (female participant) should be according to the following schedule:

Tracking of pregnancy cases occurs until after Expected Delivery Date (EDD) for all prospective pregnancy cases received from clinical studies (including pregnancies where the participant was exposed to placebo and pregnancies due to the conduct of the study).

- EDD + 1 month (mandatory for all cases). Requesting the pregnancy outcome and other clinically relevant pregnancy data or changes in data.
- EDD + 2 month (mandatory if no answer is obtained after request at EDD+1 month). A reminder letter for the outcome.
- The follow-up at EDD + 3 months is mandatory for all cases of live birth. Information on the status of the baby 3 months after delivery and information on any development issue or abnormality that would not be seen at birth must be collected.

[redacted]

- The follow up at EDD + 12 months is mandatory for all cases of live birth. Information on the status of the baby 12 months after delivery and information on any development issue or abnormality that would not be seen at birth must be collected. If the pregnancy case is lost to follow-up (e.g., no response after 3 attempts) this information must be transferred to the Safety Desk of the Country participant Safety.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

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

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

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

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

There has been no safety signal for liver toxicity with secukinumab to date in clinical trial participants who were 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 Section 16.1.

10.2.2 Renal safety monitoring

There has been no safety signal for nephrotoxicity with secukinumab in clinical trial participants who were exposed, and from a mechanism of action standpoint, there is no known effect of blocking IL-17A on the kidney. All participant with laboratory tests containing clinically

[redacted]

significant abnormal values (see Section 16.1 for notable laboratory values) are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined. Standard renal function tests (blood urea nitrogen, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

11 Data Collection and Database management

11.1 Data collection

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

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

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

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

11.2 Database management and quality control

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

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

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment(s) dispensed to the participant and all dosage changes will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

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

[redacted]

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

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. 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 participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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

12 Data analysis and statistical methods

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

Summary statistics for continuous variables will generally include the number of participants (N), minimum, lower quartile, mean, standard deviation (SD), median, upper quartile, and maximum. For categorical or binary variables, the number and percent of participants in each category will be presented.

In case of a global health disruptive event, such as pandemic/epidemic (e.g., COVID-19), affecting the ability of the participant or the site to adhere to protocol requirements and

[redacted]

assessments and therefore leading to a potential increase in the number of missing measurements, additional analysis populations may be defined as per the instructions and procedures outlined in Section 16.9.

The efficacy evaluation of secukinumab relative to placebo will generally focus on the first 16 weeks of treatment unless otherwise specified.

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

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

- Secukinumab 150 mg regimen
- Placebo regimen

Note that the treatment groups above for a participant may differ depending on the time period of the analysis and whether one assesses the participant for efficacy or safety (see Section 12.1 for details). Data may be presented by a combination of the 'original' and 'switch' treatment groups. These treatment groups represent the treatment combinations the participants experience over the course of the entire trial (e.g., placebo participants who are reassigned to secukinumab 150 mg, non-responders who are escalated to secukinumab 300 mg).

12.1 Analysis sets

The following analysis sets will be used in this study:

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

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

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

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

12.2 Participant 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:

[redacted]

- Participant's global assessment of disease activity and other ASAS components, hsCRP (mg/L and >ULN), [redacted], prior use (yes/no) of TNF-α 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), [redacted] 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 participants with pre-solicited cardiovascular risk factors will be summarized by treatment group. The number of cardiovascular risk factors that each participant has will also be summarized by treatment group. If it is unknown whether or not a participant currently or previously experienced a specific cardiovascular risk factor, it will be assumed that cardiovascular risk factor did not occur for that participant.

12.3 Treatments

Study treatment

The analysis of study treatment data will be based on the safety set. The number of visits with active and placebo 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 participants with cumulative exposure levels (e.g., any exposure, ≥ 1 weeks, ≥ 2 weeks, ≥ 3 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 the 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 participants receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

[redacted]

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

Prior surgeries and procedures are defined as surgeries and procedures done prior to first dose of study treatment. Any surgeries and procedures done between the day of first dose of study treatment and within 84 days after the last dose will be a concomitant surgeries and procedures, including those which were started pre-baseline and continued into the period where study treatment is administered.

The number and percentage of participants receiving prior and concomitant nr-axSpA therapy will be presented by randomized treatment group as well as the reasons for stopping their therapies (primary lack of efficacy, secondary lack of efficacy, lack of tolerability, other) and the total duration of exposure to nr-axSpA therapies previously. NSAID, glucocorticoid and DMARD (MTX, Leflunomide, Sulfasalazine) use will be summarized.

12.4 Analysis of the primary endpoints/estimands

The primary objective of this study is to assess the efficacy of secukinumab relative to placebo at week 16 based on the proportion of participants achieving an ASAS40 response in TNF-α naïve participants. The consistency of the treatment difference between this bridging study and the global study will be evaluated.

12.4.1 Definition of primary endpoints/estimands

The primary efficacy variable is response to treatment according to the ASAS40 criteria at Week 16 in TNF-α naïve participants with active nr-axSpA. The analysis of the primary variable will be based on the FAS participants.

12.4.2 Statistical model, hypothesis, and method of analysis

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. Difference in response proportions between secukinumab regimen and placebo regimen and the corresponding 95% confidence interval (CI) will be computed utilizing the logistic regression model fitted.

12.4.3 Handling of missing values/censoring/discontinuations

Missing data for ASAS40 response and other binary efficacy variables (e.g., ASAS5/6, etc.) for data up to Week 16 will be handled as follows:

1. Participants who discontinue from treatment or study for any reason will be considered as non-responders from the time of discontinuation through Week 16
2. Participants 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.

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

[redacted]

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

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

12.4.4 Sensitivity analyses for primary endpoint/estimand

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

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

The impact of missing data on the analysis results of ASAS40 in active nr-axSpA participants will be assessed as well by repeating the logistic regression model using different ways to handle missing data. These may include, but are not limited to:

- Multiple imputation
- Observed data analysis

12.4.5 Supplementary analysis

[redacted]

Subgroup analysis of the primary endpoint will be conducted by stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and selected subgroup groups. The subgroups to be considered will be defined in the Statistical Analysis Plan (SAP).

[redacted]

12.5 Analysis of secondary endpoints/estimands

12.5.1 Efficacy and/or Pharmacodynamic endpoints

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

ASAS40 at Week 16

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

ASAS 5/6 at Week 16

The proportion of participants meeting the response criteria will be evaluated using a logistic regression model with treatment group and stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) 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+) 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.

BASDAI50 at Week 16

The proportion of participants meeting the response criteria at Week 16 will be evaluated using a logistic regression model with treatment group and stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) as factors and baseline weight and baseline 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+) and analysis visit as factors and $\log_e$ baseline hsCRP and weight as continuous covariates. Treatment by analysis visit and $\log_e$ baseline hsCRP by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. The estimate and the 2-sided 95% confidence intervals obtained from the model will be back transformed to the original scale.

[redacted]

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+) 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.

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+) as factors, and weight and baseline inflammation score as covariates.

ASAS20 at Week 16

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

SF-36 PCS at Week 16

See Section 12.5.4 Patient Reported Outcomes.

ASQoL at Week 16

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

ASAS partial remission at Week 16

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

12.5.2 Safety endpoints

Adverse events

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

[redacted]

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of participants 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 participant reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a participant reported more than one adverse event within the same primary system organ class, the participant will be counted only once with the greatest severity at the system organ class level, where applicable. Serious adverse events will also be summarized.

These summaries may be presented separately by different study periods, e.g., Week 1-16 and entire treatment period.

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

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

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

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

Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology and serum chemistry). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from baseline will only be summarized for participants 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 participant's baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. These summaries will be presented by laboratory test and treatment group. Shifts will be presented by visit as well as for most extreme values post-baseline.

[redacted]

[redacted]

Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented

[redacted]

by vital sign and treatment group. Change from baseline will only be summarized for participants 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.

[redacted]

12.5.5 Patient reported outcomes

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

BASDAI

The following variables will be evaluated:

- BASDAI
- BASDAI50

See Section 12.5.1 Efficacy and/or Pharmacodynamic endpoints for details.

BASFI

See Section 12.5.1 Efficacy and/or Pharmacodynamic endpoints.

[redacted]

Patient's global assessment of disease activity (VAS)

Summary statistics of observed data by visit and change from baseline in patient's global assessment of disease activity will be provided for each treatment.

Patient's assessment of back pain intensity (VAS)

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

SF-36

The following variables will be evaluated:

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

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

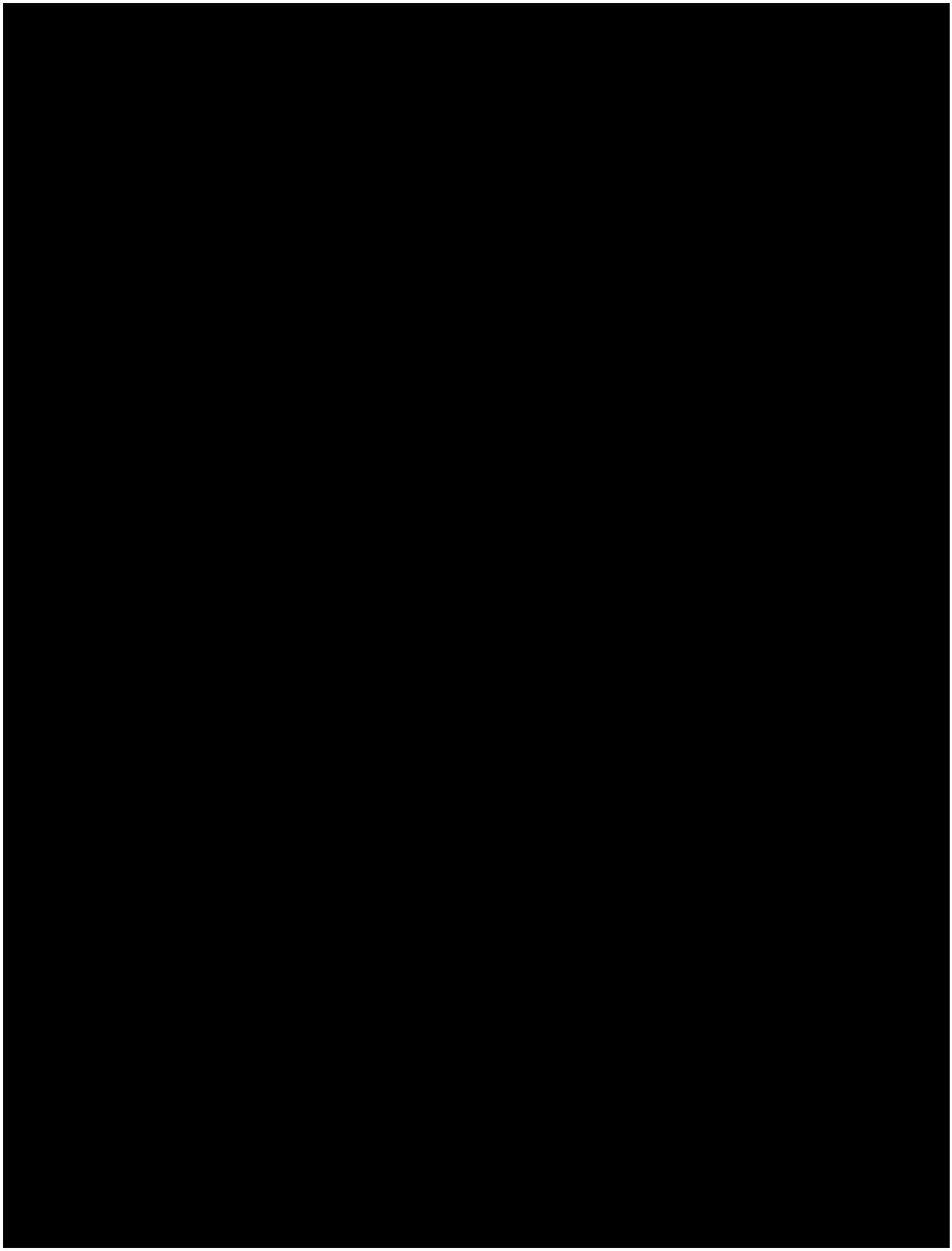
For the responder analyses, the proportion of responders will be descriptively summarized along with its 95% CI for each randomized treatment based on observed data.

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

ASQoL

See Section 12.5.1 Efficacy and/or Pharmacodynamic endpoints.

[redacted]



[redacted]

12.7 Interim analyses

Not applicable.

12.8 Sample size calculation

12.8.1 Primary endpoints

As it is a bridging study for China registration, this study will pursue an estimation strategy rather than formal hypothesis testing of treatment difference.

[redacted]

Analysis of an unpublished phase III study with secukinumab in nr-axSpA showed a placebo response rate of about 29.2% and a secukinumab 150 mg response rate of 41.5% after 16 weeks for ASAS40 in TNF-α naïve participants. Assuming 10% of randomized participants will be TNF-α IR and 90% of randomized participants will be TNF-α naïve. With 134 participants, 120 of them are TNF-α naïve (1:1 ratio to two groups), then there are approximately 77.3% probability to show at least 50% global treatment difference (6.15%) and approximately 90.7% probability to show positive treatment difference.

Table 12-1 Probability of Success with Different Observed Response Rates of ASAS40 in TNF-α naïve participants

	Observed Response Rate				Criterion 1		Criterion 2	
	Secukinumab (p_1)	Placebo (p_2)	p_1-p_2	95% CI of (p1-p2)	Aimed Treatment Difference	PoS	Aimed Treatment Difference	PoS
Scenario 1	0.395	0.292	0.103	(-0.066, 0.272)	> 0.0615	0.699	> 0	0.864
Scenario 2	0.415	0.292	0.123	(-0.046, 0.293)	> 0.0615	0.773	> 0	0.907
Scenario 3	0.435	0.292	0.143	(-0.027, 0.313)	> 0.0615	0.835	> 0	0.939
Scenario 4	0.455	0.292	0.163	(-0.008, 0.334)	> 0.0615	0.885	> 0	0.962

12.9 Primary endpoint analysis

The primary endpoint analysis will be performed after all participants have completed the Week 16 visit. The investigators, site personnel and monitors will continue to remain blinded to the original treatment assignment that each participant received at randomization until after the database lock for Week F60 analysis. The primary endpoint analysis will be used for regulatory submission.

Subsequent to the primary endpoint analysis, the final analysis is planned after participants have completed the Week F60 assessments and may be used for regulatory submission and/or publication purposes. Additional analyses may be performed to support interactions with health authorities, as necessary.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g.,

[redacted]

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

13.3 Publication of study protocol and results

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

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that will be provided to you at the investigator portal.

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

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

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by

[redacted]

Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

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

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

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

[redacted]

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[redacted]

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

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

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

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

Final Harmonization		
	Notable Criteria	
Laboratory Variable	**Standard Units**	**SI Units**
LIVER FUNCTION AND RELATED VARIABLES		
SGOT (AST)	>3 x ULN	>3 x ULN
SGPT (ALT)	>3 x ULN	>3 x ULN
Bilirubin	>2 x ULN	>2 x ULN
Alkaline phosphatase	>2.5 x ULN	>2.5 x ULN
RENAL FUNCTION VARIABLES		
Creatinine (serum)	>2 x ULN	>2 x ULN
Blood Urea Nitrogen (BUN)	≥ 5 × ULN	≥ 5 × ULN
HEMATOLOGY VARIABLES		
Hemoglobin	20 g/L decrease from baseline	
Platelet Count	<100x10E^9/L	
White blood cell count	<0.8 x LLN	
Neutrophils	<0.9 x LLN	

SGOT (AST) = serum glutamic oxaloacetic transaminase (aspartate aminotransferase), SGPT (ALT) = serum glutamic pyruvic transaminase (alanine aminotransferase), LLN=lower limit of normal, ULN=upper limit of normal, SI Unit = The International System of Units

[redacted]

16.2 Blood collection log

Refer to the central laboratory manual for sample collection, preparation and shipping information.

[redacted]

16.3 Modified New York criteria

According to Exclusion Criteria 1, participants meeting clinical criteria 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.

[redacted]

16.4 ASAS Classification Criteria for Axial Spondyloarthritis (axSpA)

ASAS Classification Criteria for Axial Spondyloarthritis (axSpA)

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	

16.5 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:

[redacted]

6. C-reactive protein (acute phase reactant)

16.5.1 Bath Ankylosing Spondylitis Functional Index (BASFI)

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

16.5.2 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:

[redacted]

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 participants 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).

[redacted]

[redacted]

16.6 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.

[redacted]

16.8 Guidelines for administering the questionnaires for patient reported outcomes

Before trial start

Study coordinators should familiarize themselves with the PRO questionnaires in the trial and identify any items where a participant'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 participant responds 'most or all of the time', then the study coordinator should inform the study investigator.

Before completion

Participants should be provided with the correct questionnaire at the appropriate visits and in the appropriate language

Participants should have adequate space and time to complete the forms

Questionnaire should be administered before the clinical examination

During completion

Administrator may clarify the questions but should not influence the response

Only one response for each question

Also see "Addressing Problems and Concerns"

After completion

Check for completeness and not for content*

Check for multiple responses that were made in error

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

Addressing problems and concerns

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

The participant does not want to complete the questionnaires

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

The participant is too ill or weak to complete the questionnaires

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

The participant wants someone else to complete the questionnaires

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

The participant does not want to finish completing the questionnaires

If non-completion is a result of the participant having trouble understanding particular items, ask the participant 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 participant.

[redacted]

The participant 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 participant that his/her answers will be pooled with other participants' answers and that they will be analyzed as a group rather than as individuals. Tell the participant 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 participant asks the meaning of a question/item

While completing the questionnaire, some participants might ask the meaning of specific items so that they can better understand and respond. If this happens, assist the participant by rereading the question for them *verbatim.* If the participant 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. Participants should answer the questions based on what *they* think the questions mean.

General information about all questionnaires

All questionnaires have to be completed by the participants in their local languages using an electronic device. The questionnaires should be completed by the participants in a quiet area free from disturbance, and before any visit assessments. Participants 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 participant's responses without influencing their answers. The information provided is strictly confidential and will be treated as such. If a participant has missed a question or given more than one response per question, then this should be brought to participant. Incomplete questions should not be accepted without first encouraging the participant to complete unanswered questions.

The investigator must complete the participant/visit information on the electronic device and ensure that the center number, participant'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 participant/visit information.

16.9 Guidance of Study management during potential future pandemic/epidemic

Scope

The instructions and procedures outlined in this appendix are applicable only in case of global health disruptive event, such as pandemic/epidemic [e.g. severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease/COVID-19]. In order to maintain the study data integrity and ensure the safety of participants, investigators should inform and discuss with the sponsor's monitor about its applicability prior to implementing any of the following procedures.

[redacted]

Screening (Screening to Randomization)

In case of a global health disruptive event, such as pandemic/epidemic (e.g. COVID-19), affecting the ability of the participant or the site to adhere to protocol requirements and assessments, investigators should only randomize participants if they expect them to be able to adhere to assessments and protocol-related activities. Evaluation of the eligibility of the participant should consider the ability to attend study visits and adhere to protocol assessments. If the latter is not anticipated, screening and randomization should not proceed, and re-screening (as allowable per protocol) should be considered when conditions allow for proper trial management.

During Treatment Period (Baseline to EOT)

In case of a global health disruptive event, such as pandemic/epidemic (e.g. COVID-19), affecting the ability of the participantor the site to adhere to protocol requirements and assessments and therefore leading to a potential increase in the number of missing measurements, the Sponsor may consider recruiting additional participants to restore the sample size only after consultation with local regulatory authority.

Risks and Benefits

Active infection should be excluded in order to comply with eligibility criteria (see Section 5.2).

The potential of secukinumab to increase the risk of infections has been identified (see IB Section 7.1). COVID-19 has similar impact on risk-benefit as other infections. No additional risk is anticipated due to COVID-19 infection.

Visits

If the COVID-19 pandemic or similar situations that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented only for the visits outlined in the table above. Phone calls, virtual contacts (e.g. teleconsult) or visits by site staff to the participant´s home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic until it is safe for the participant to visit the site again. Any safety or efficacy assessments, which could not be feasible to perform or evaluate conduct remotely or virtually, the protocol deviation need to be recorded. Such data will treated as missing data.

This **will not** apply to Screening, BSL, all clinic visits up to including Week 16, Week 24, Week 52 and Week 60 visit. For remaining visits per protocol, the above exceptions may be implemented, however, every effort need to be made to ensure on-site visit. If on-site visit is prevented at Screening or Baseline visit, the participants should not be randomized.

Laboratory assessments

If the designated central laboratory is unable to operate, collection of samples may be modified by Novartis and if modified, will be communicated to the investigator. In such cases, it is acceptable to collect and perform laboratory tests at local laboratories that are certified for these

[redacted]

diagnostics. Similarly, sites should inform to the Sponsor of proposed changes to sample management/collection.

IMP (administration and dispensation)

In case of a major health care event (e.g., COVID-19 pandemic, epidemic) that limits or prevents on-site study visits, delivery of IMP directly to a participant's home is generally permitted (if allowed by local regulations) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. For changes in the distribution of trial drugs, the primary goal is to provide IMP to participants based on protocol to ensure participant safety and the integrity of clinical trials. Implementation will need to be discussed with Novartis. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 1-month supply. In this case, regular phone calls or virtual contacts (every 4 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, and discussion of the participant´s health status until the participants can again visit the site.

IMP home administration is allowed only for the scheduled dosing visits (outlined in Table 8-1) if the participant or caregiver is trained on subcutaneous self-administration.

Changes in transportation and storage arrangements will not violate the blind design of treatment. The investigator should make relevant records such as the inventory and storage conditions of trial drugs.

Efficacy and Clinical Outcomes Assessments (COAs)

In the event of a pandemic/epidemic that limits or prevents on-site study visits, selected efficacy assessments including Patient Reported Outcomes (PROs) can alternatively be done via web-based backup portal or visits of site staff to the participant´s home, depending on local regulations and capabilities, and following any applicable training in the required process.

Exceptionally, if the electronic device is not working, the efficacy assessments and Patient Reported Outcomes may be completed using web-based backup portal for PROs. The data would then be transcribed in the vendor database.

For individual cases where the efficacy endpoint is not collected, the reasons for not obtaining the efficacy evaluation should be documented.

Imaging

During the COVID-19 pandemic that limits or prevents on-site study visits, the collection of images may be modified by Novartis and will be communicated to the investigator.

[redacted]

Safety

During the COVID-19 pandemic that limits or prevents on-site study visits, regular phone or virtual calls will occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until the participant can again visit the site.

Female participants would be advised to perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment.

Informed Consent Procedures

During the COVID-19 pandemic that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference). Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.). Remote informed consent should be appropriately documented and confirmed by way of standard informed consent procedures at the earliest opportunity when the participant will be back at the trial sites.

Site monitoring

In the event of a major health care disruption (e.g. pandemic, epidemic), requiring social distancing or limited travel/attendance to the clinical trial site, remote site initiation and monitoring could be considered.

Note: The details on operationalizing above-mentioned study management aspects during potential future pandemic/epidemic will be supplemented by study specific guidance to the clinical trial sites.

[redacted]