NOVARTIS

Clinical Development - Medical Affairs Region Europe

AIN457/Secukinumab

Protocol CAIN457F3302 / NCT02721966

MAXIMISE (Managing AXIal Manifestations in Psorlatic Arthritis with SEcukinumab), a randomized, double-blind, placebo-controlled, multicenter, 52-week study to assess the efficacy and safety of secukinumab 150 mg or 300 mg s.c. in patients with active psoriatic arthritis and axial skeleton involvement who have inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs)

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ALP	Alkaline phosphatase
ALT/SGPT	Alanine aminotransferase/serum glutamic pyruvic transaminase
ANCOVA	Analysis of covariance
AS	Ankylosing spondylitis
ASAS	Assessment of spondyloarthritis international society
[redacted]	[redacted]
[redacted]	[redacted]
AST/SGOT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase
ATC	Anatomical therapeutic classification
AxPsA	Axial psoriatic arthritis (i.e. psoriatic arthritis with axial involvement)
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
BASRI	Bath ankylosing spondylitis radiology index
bpm	Beats per minute
CASPAR	Classification criteria for psoriatic arthritis
CI	Confidence interval
COX	Cyclo-oxygenase
CPO	Country pharma organization
CRO	Contract research organization
CRF	Case report form
[redacted]	[redacted]
CQA	Compliance Quality Assurance
DAR	Drug administration record
DMARD(s)	Disease modifying anti-rheumatic drug(s)
eCRF	electronic case report/record form
ECG	Electrocardiogram
EDC	Electronic data capture
EMA/EMEA	European Medicines (Evaluation) Agency
EOS	End of study
EULAR	European league against rheumatism
FACIT-Fatigue©	Functional assessment of chronic illness therapy fatigue scale
FAS	Final analysis set
GCP	Good clinical practice
GGT/γGT	Gamma glutamyl transferase
GRAPPA	Group for research and assessment of psoriasis and psoriatic arthritis
HAQ-DI©	Health assessment questionnaire – disability index
hCG	human chorionic gonadotropin
HIV	Human immunodeficiency virus
HLA-B27	Human leukocyte antigen B27
[redacted]	[redacted]

[redacted]

IB	Investigator brochure
IBP	Inflammatory back pain
ICH	International conference on harmonization of technical requirements for registration of pharmaceuticals for human use
ICF	Informed consent form
IEC	Independent Ethics Committee
IFU	Instructions for use
IL	Interleukin
IN	Investigator notification
INR	International normalized ratio (for blood clotting time)
IRB	Institutional Review Board
IRT	Interactive response technology
i.v.	intravenous(ly)
LFT	Liver function test (raised serum transaminases and/or bilirubin levels)
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MRMM	Mixed-effects repeated measures model
[redacted]	[redacted]
MRI	Magnetic resonance imaging
m-SASSS	modified Stoke ankylosing spondylitis spinal score
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
[redacted]	[redacted]
PCR	Protein-creatinine ratio
PFS	Prefilled syringe
PPD	Premature patient discontinuation
PRN	Pro re nata (as needed)
PRO	Patient reported outcome
PsA	Psoriatic arthritis
PT	Prothrombin time
QFT	QuantiFERON tuberculosis gold test
QM	Quality management
RA	Rheumatoid arthritis
SAE	Serious adverse event
s.c.	Subcutaneous(ly)
SDI	Standard disability index
SJC	Swollen joint count
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SUSAR(s)	Suspected unexpected serious adverse reaction(s)
TB	Tuberculosis
TBL	Total bilirubin
TJC	Tender joint count

[redacted]

TNF	Tumor necrosis factor
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cell

[redacted]

Glossary of terms

Control drug	Drugs(s) 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.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol).
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Medication number	A unique identifier on the label of each study drug package in studies that dispense medication using an interactive response technology (IRT) system.
Mis-randomization	A patient who is randomized to a treatment group, but did not receive any study treatment.
Patient number	A number assigned to each patient who is screened for the study.
Period	The planned stage of the patient's participation in the study. Each period serves a purpose in the study as a whole. In this study, there is a Screening period for determination of patient eligibility, Period 1, which is a 12-week double-blind placebo-controlled period; and Period 2, which is 36-week double-blind active treatment period.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned, unless the patient is followed for progression and/or survival.
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 patient, corresponding to a specific treatment arm assignment.
Re-randomization	In this study, patients randomized to placebo at Baseline will be re-randomized (1:1 ratio) to secukinumab 150 mg or 300 mg at Week 12.
Re-screening	A patient who qualified for all or most eligibility criteria but could not be randomized within the Screening period can be considered for re-screening only once.
Rescue medication	Any new therapeutic intervention or a significant change to ongoing therapy made because a patient is experiencing either no benefit from participation in the trial or worsening/ exacerbation of their disease.
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug, placebo or background therapy.
Study treatment discontinuation	When the patient permanently stops taking study treatment prior to the defined study treatment completion date.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study.

[redacted]

Amendment Rationale

[redacted] It was decided not to perform the X-ray assessments in order to reduce the complexity of the study and to focus on the existing primary and secondary objectives. The Introduction (Section 1.1), the Study objectives and endpoints (Section 2.4), the Study design (Figure 3-1), the Visit schedule (Table 6-1) and assessments (Section 6.4), and the Data analysis (Section 9.6) have been updated accordingly.

Additionally, this protocol amendment includes the correction of typographical errors, formatting errors and editorial changes to increase clarity and consistency of the text. Consequently changes were incorporated directly in the protocol with track changes, even if not listed specifically in this section.

The first patient is planned to be recruited in the study on 30 September 2016.

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

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary

Protocol number	CAIN457F3302
Title	MAXIMISE (Managing AXIal Manifestations in PsorIatic Arthritis with SEcukinumab), a randomized, double-blind, placebo-controlled, multicenter, 52-week study to assess the efficacy and safety of secukinumab 150 mg or 300 mg s.c. in patients with active psoriatic arthritis and axial skeleton involvement who have inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs)
Brief title	Study of the efficacy and safety of secukinumab in patients with active psoriatic arthritis with axial skeleton involvement (AxPsA).
Sponsor and clinical phase	Novartis and Phase 3b
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to demonstrate the efficacy and safety of secukinumab 150 mg or 300 mg in the management of axial manifestations in PsA patients who have failed to respond to at least 2 NSAIDs over a 4-week period, according to assessment of spondyloarthritis international society (ASAS) recommendations for the treatment of axial spondyloarthritis (AxSpA). In particular, the study will provide evidence on the ability of secukinumab 150 mg or 300 mg to improve clinical [redacted] outcomes in patients with AxPsA.
Primary objective	• To demonstrate that secukinumab 300 mg s.c. is superior to placebo in the achievement of ASAS 20 response at Week 12.
Key secondary objective	• To demonstrate that secukinumab 150 mg s.c. is superior to placebo in the achievement of ASAS 20 response at Week 12 after superiority of 300 mg is established.
Secondary objectives	• To evaluate secukinumab 300 mg s.c. versus placebo in the achievement of ASAS 40 at Week 12. • To evaluate secukinumab 150 mg s.c. versus placebo in the achievement of ASAS 40 at Week 12. • To evaluate secukinumab 300 mg s.c. versus placebo in the achievement of Bath ankylosing spondylitis disease activity index (BASDAI) 50 at Week 12. • To evaluate secukinumab 150 mg s.c. versus placebo in the achievement of BASDAI 50 at Week 12. • To evaluate secukinumab 300 mg s.c. versus placebo in the reduction of spinal pain measured by visual analog scale (VAS) at Week 12. • To evaluate secukinumab 150 mg s.c. versus placebo in the reduction of spinal pain measured by VAS at Week 12. • To evaluate secukinumab 300 mg s.c. versus placebo in achieving an improvement in Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index at Week 12. • To evaluate secukinumab 150 mg s.c. versus placebo in achieving an improvement in SPARCC enthesitis index at Week 12. • To evaluate secukinumab 300 mg s.c. versus placebo in achieving an improvement in health assessment questionnaire disability index (HAQ-DI©) at

[redacted]

	Week 12. • To evaluate secukinumab 150 mg s.c. versus placebo in achieving an improvement in HAQ-DI© at Week 12. • To evaluate secukinumab 300 mg s.c. versus placebo in achieving an improvement in the functional assessment of chronic illness therapy fatigue scale (FACIT-Fatigue©) at Week 12. • To evaluate secukinumab 150 mg versus placebo in achieving an improvement in the FACIT-Fatigue© at Week 12. • To evaluate secukinumab 300 mg s.c. versus placebo in achieving an improvement in the ASAS health index at Week 12. • To evaluate secukinumab 150 mg s.c. versus placebo in achieving an improvement in the ASAS health index at Week 12. • To evaluate secukinumab 300 mg s.c. versus placebo based on the proportion of patients achieving an American College of Rheumatology (ACR) 20 response at Week 12. • To evaluate secukinumab 150 mg s.c. versus placebo based on the proportion of patients achieving an ACR 20 response at Week 12. • To evaluate the safety and tolerability of secukinumab.

[redacted]

Study design	This is a 52-week, randomized, double-blind, double-dummy, placebo-controlled, multicenter study to assess the efficacy of secukinumab 150 mg or 300 mg in patients with AxPsA who have had an inadequate response to 2 different NSAIDs. The study will consist of 2 treatment periods; a double-blind placebo-controlled period from Baseline to Week 12 followed by a double-blind secukinumab treatment period from Week 12 to Week 52.
Population	Male and female patients ≥ 18 years of age with PsA fulfilling the classification criteria for psoriatic arthritis (CASPAR) and who are naïve to biologic treatment. Patients must have clinical signs of spinal involvement defined by presence of inflammatory back pain (IBP) with active disease defined by BASDAI score ≥ 4, spinal pain visual analog scale (VAS) ≥ 40 (0 to 100 mm scale) and inadequate response to at least 2 NSAIDs over a 4-week period. Patients may continue pre-study NSAIDs, methotrexate (MTX) and corticosteroids from Baseline through to the end of study (NSAID, MTX and corticosteroid doses must be stable from Baseline to Week 12).
Key inclusion criteria	Patients eligible for inclusion in this study have to fulfill all of the following criteria: 1. Patients must be able to understand and communicate with the investigator and comply with the requirements of the study and must provide a written, signed and dated informed consent before any assessment is performed. 2. Male or non-pregnant, non-lactating female patients of at least 18 years of age. 3. Diagnosis of PsA classified by CASPAR criteria. 4. Active spinal disease defined by BASDAI score ≥ 4. 5. Spinal pain as measured by VAS ≥ 40 at Baseline (0 to 100 mm scale). 6. Inadequate response to at least 2 NSAIDs over a 4-week period (at least).
Key exclusion criteria	Patients fulfilling any of the following criteria are not eligible for inclusion in this study: 1. Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process obtained within 3 months prior to Screening and evaluated by a qualified physician. 2. Patients taking high potency opioid analgesics (e.g. methadone, hydromorphone, morphine). 3. History of exposure to other IL-17 or IL-23 inhibitor biologic drug(s). 4. History of exposure to previous biologic disease modifying anti-rheumatic drug(s) (DMARD(s)) (tumor necrosis factor (TNF) blockers or ustekinumab). 5. Current treatment with DMARD(s) other than MTX. 6. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization. 7. Patients regularly taking NSAIDs as part of their PsA therapy who are not on a stable dose for at least 2 weeks before study randomization. 8. Patients regularly taking systemic corticosteroids as part of their PsA therapy who

[redacted]

	are not on a stable dose ≤ 10 mg/day of prednisone or equivalent for at least 2 weeks before randomization. 9. Patients who are on MTX (≤ 25 mg/week) who are not on a stable dose for at least 4 weeks before randomization. 10. Patients on MTX who are not on folic acid supplementation at randomization. 11. Patients who are on DMARD(s) other than MTX who have not discontinued the DMARD(s) 4 weeks prior to the randomization visit, or 8 weeks prior to randomization for patients on leflunomide unless a cholestyramine washout has been performed (in which cases 4 weeks applies). 12. Active ongoing inflammatory diseases other than PsA (e.g. inflammatory bowel disease) that might confound the evaluation of the benefit of secukinumab therapy. [redacted] 14. Any intramuscular or intravenous (i.v.) corticosteroid treatment within 4 weeks before randomization. 15. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g. CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19).
Study treatment	Secukinumab 150 mg will be provided in 1 mL prefilled syringes (PFS) for s.c. injection. Secukinumab 300 mg will be provided as 2 PFS each containing 150 mg secukinumab. Secukinumab placebo will be provided in 1 mL PFS. At Baseline, all patients whose eligibility is confirmed will be randomized in a 1:1:1 ratio to secukinumab 150 mg (Group 1), secukinumab 300 mg (Group 2) or placebo (Group 3). At Week 12, patients randomized to placebo at Baseline (i.e. Group 3) will be re-randomized in a 1:1 ratio to active treatment with secukinumab 150 mg or secukinumab 300 mg. **Group 1: secukinumab 150 mg** Treatment Period 1 • secukinumab 150 mg (1 × 1.0 mL PFS) + placebo (1 × 1.0 mL PFS) at Baseline, Week 1, 2, 3 and 4, then 4 weeks later at Week 8 Treatment Period 2 • secukinumab 150 mg (1 × 1.0 mL PFS) + placebo (1 × 1.0 mL PFS) administered every 4 weeks from Week 12 to Week 52 (last dose on Week 48) **Group 2: secukinumab 300 mg** Treatment Period 1 • secukinumab 300 mg (2 × 1.0 mL PFS) administered at Baseline, Week 1, 2, 3 and 4, then 4 weeks later at Week 8. Treatment Period 2 • secukinumab 300 mg (2 × 1.0 mL PFS) administered every 4 weeks from Week 12 to Week 52 (last dose on Week 48) **Group 3: placebo** Treatment Period 1 • placebo (2 × 1.0 mL PFS) administered at Baseline, Week 1, 2, 3 and 4, then 4 weeks later at Week 8.

[redacted]

	Treatment Period 2 • secukinumab 150 mg (1 × 1.0 mL PFS) + placebo (1 × 1.0 mL PFS) administered every 4 weeks from Week 12 to Week 52 (last dose on Week 48), OR • secukinumab 300 mg (2 × 1.0 mL PFS) administered every 4 weeks from Week 12 to Week 52 (last dose on Week 48) Patients will be allowed to continue background medications with MTX, NSAIDs and corticosteroids from Baseline until the end of study. The dose must be stable from Baseline to Week 12, and is recommended to continue at a stable dose from Week 12 to Week 52/end of study. In patients taking NSAIDs, the NSAID intake will be recorded according to ASAS recommendations up to Week 52.
Efficacy assessments	• Assessment of spondyloarthritis international society (ASAS) responses • Bath ankylosing spondylitis disease activity index (BASDAI) • Bath ankylosing spondylitis functional index (BASFI) • Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index • American College of Rheumatology 20 (ACR 20) • Spinal pain (VAS) [redacted]
Key safety assessments	• Evaluation of adverse events (AEs)/serious adverse events (SAEs) • Physical examination • Vital signs • Laboratory evaluations (hematology, clinical chemistry, urinalysis)
Other assessments	Patient reported outcomes (PROs): • Health assessment questionnaire – disability index (HAQ-DI©) • Functional assessment of chronic illness therapy fatigue scale (FACIT-Fatigue©) • ASAS health index Note: The BASDAI, a PRO assessing disease activity, and BASFI, a PRO assessing functional limitation, which are part of ASAS are described under efficacy assessments
Data analysis	The primary endpoint in the study is ASAS20 at Week 12. The testing hierarchy tests secukinumab treatments versus placebo for the primary endpoint at Week 12 for the full analysis population. The statistical hypothesis for ASAS 20 being tested is that there is no difference in the proportion of patients fulfilling the ASAS 20 criteria at Week 12 in the secukinumab groups versus placebo group. The primary analysis will be conducted via logistic regression with treatment and concomitant MTX intake status as factors. Odds ratios, 95% confidence interval (CI) and p-values will be presented comparing each secukinumab group to placebo.
Key words	ASAS, PsA, axial, MRI

[redacted]

1 Introduction

1.1 Background

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis, usually seronegative for rheumatoid factor, which can affect peripheral and/or axial joints. Axial PsA (AxPsA) is PsA involving the axial joints and ties PsA to the concept of spondyloarthritis (SpA) (Biagoni et al 2014). There is wide variability (25% to 70%) in the reported prevalence of axial involvement in PsA due to differences in the criteria used for defining AxPsA (Gladmann et al 2007). AxPsA can affect the sacroiliac joints, as well as the lumbar, thoracic, and cervical spine. Some radiographic features of AxPsA are similar to those found in ankylosing spondylitis (AS) although patients with AS generally have more severe radiographic damage compared to AxPsA (Biagoni et al 2014). AxPsA may be distinguished from AS in terms of radiographic features of asymmetrical sacroiliitis, non-marginal and asymmetrical syndesmophytes, paravertebral ossification, and frequent involvement of the cervical spine (Biagoni et al 2014, Helliwell et al 1998). These distinguishing features of AxPsA mean there is a medical need to evaluate current treatment for PsA/AS in isolation for this sub-population.

Conventional X-ray scores used to assess spinal involvement in PsA, such as the Bath ankylosing spondylitis radiology index (BASRI) and the modified Stoke ankylosing spondylitis spinal score (m-SASSS), have been designed for AS and do not encompass some radiological features of AxPsA (Biagioni et al 2014, Lubrano et al 2009).

[redacted]

According to European League Against Rheumatism (EULAR) recommendations for the management of PsA with pharmacological therapies, non-steroidal anti-inflammatory drugs (NSAIDs) should be used as the first-line treatment in the majority of PsA patients (Gossec et al 2015). NSAIDs have been shown to be efficacious with regard to joint symptoms in patients with PsA but have not shown efficacy with regard to skin lesions. The latest GRAPPA treatment guidelines for axial disease (Coates et al 2016) are derived from diagnostic criteria, screening, monitoring and response to therapy in AS since these data are

[redacted]

not available for AxPsA. The guidelines recommend initiation of tumor necrosis factor (TNF) inhibitors for patients with axial symptoms who have not responded to NSAIDs, physiotherapy, and sacroiliac injections (when appropriate). Disease modifying anti-rheumatic drug(s) (DMARDs) are not deemed effective in this population with no evidence available for efficacy of sulfasalazine in axial disease within PsA or AS (Chen et al 2014). GRAPPA conditionally recommends NSAIDs for patients with an inadequate response to TNF inhibitors usually as an adjunct to further therapy on the basis of observational data for other disease domains (Coates et al 2016). The effectiveness of biologics in the treatment of AxPsA has been poorly assessed and so there is an unmet need for further clinical studies of biologics in patients with AxPsA.

The Assessment of SpondyloArthritis international Society (ASAS) has focused in the last years in defining measuring treatment response in clinical trials, and provided validated ASAS-endorsed response criteria for SpA. The ASAS response criteria are built on the basis of a core set of domains which includes function, pain, spinal mobility, patient global, peripheral joints and entheses, stiffness, fatigue and acute phase reactants (Sieper et al 2009). The primary endpoint of the present study is represented by the ASAS 20 improvement criteria which implies the improvement and no worsening of >20% and >1 unit on a scale of 10 in at least 3 out of 4 domains (patient global, pain, function, inflammation). The secondary end points of the study are the ASAS 40, which implies the improvement and no worsening of >40% and >1 unit on a scale of 10 in the same domains of ASAS 20 response, the Bath ankylosing spondylitis disease activity index (BASDAI), which is a 6 questions tool providing information on axial disease activity and the VAS assessments of Total Spine Pain which provides information on the severity of spinal pain as a general disease feature and specifically during the night.

In an observational study of patients with PsA with axial manifestations (Lubrano et al 2011), the effectiveness at 12 months of etanercept biologic therapy was assessed as per assessment of spondyloarthritis international society (ASAS) response criteria; 72% of patients had improvement in BASDAI, as well as in other outcome measures. In a Phase 3, 12-month study (Mc Innes et al 2013), the monoclonal antibody ustekinumab showed significant reduction in BASDAI 20 and 70 at the 45 mg dose and significant reduction in BASDAI 20/50/70 levels at the 90 mg dose at Week 24. The proportion of ACR 20, ACR 50 and ACR 70 responders in the ustekinumab groups was significantly greater than placebo for both the 45 mg dose and 90 mg dose at Week 24, and responses were maintained until Week 52. Significantly greater ACR 20 responses with ustekinumab compared to placebo were observed as early as Week 8 (Mc Innes et al 2013).

Secukinumab (AIN457) is a high-affinity fully human monoclonal anti-human antibody that neutralizes interleukin (IL)-17A activity, which is approved in Europe (since Nov 2015) for the treatment of patients with active PsA (based on the pivotal Phase 3 trials in PsA: CAIN457F2306 (FUTURE 1; Mease et al 2014) and CAIN457F2312 (FUTURE 2; Mc Innes et al 2015)) and patients with active AS (based on the pivotal Phase 3 trials in AS: CAIN457F2305 and CAIN457F2310 (MEASURE 1 and MEASURE 2; Baeten et al 2015)).

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[redacted]

1.2 Purpose

The purpose of this study is to demonstrate the efficacy and safety of secukinumab 150 mg or 300 mg in the management of axial manifestations in PsA patients who have failed to respond to at least 2 NSAIDs over a 4-week period, according to ASAS recommendations for the treatment of axial spondyloarthritis (AxSpA). In particular, the study will provide evidence on the ability of secukinumab 150 mg or 300 mg to improve clinical [redacted] outcomes in patients with AxPsA.

2 Study objectives and endpoints

2.1 Primary objective

To demonstrate that secukinumab 300 mg s.c. is superior to placebo in the achievement of ASAS 20 response at Week 12.

2.2 Key secondary objective

To demonstrate that secukinumab 150 mg s.c. is superior to placebo in the achievement of ASAS 20 response at Week 12 after superiority of 300 mg is established.

2.3 Secondary objectives

- To evaluate secukinumab 300 mg s.c. versus placebo in the achievement of ASAS 40 at Week 12.
- To evaluate secukinumab 150 mg s.c. versus placebo in the achievement of ASAS 40 at Week 12.
- To evaluate secukinumab 300 mg s.c. versus placebo in the achievement of BASDAI 50 at Week 12.
- To evaluate secukinumab 150 mg s.c. versus placebo in the achievement of BASDAI 50 at Week 12.
- To evaluate secukinumab 300 mg s.c. versus placebo in the reduction of spinal pain measured by visual analog scale (VAS) at Week 12.
- To evaluate secukinumab 150 mg s.c. versus placebo in the reduction of spinal pain measured by VAS at Week 12.

[redacted]

- To evaluate secukinumab 300 mg s.c. versus placebo in achieving an improvement in Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index at Week 12.
- To evaluate secukinumab 150 mg s.c. versus placebo in achieving an improvement in SPARCC enthesitis index at Week 12.
- To evaluate secukinumab 300 mg s.c. versus placebo in achieving an improvement in health assessment questionnaire disability index (HAQ-DI©) at Week 12.
- To evaluate secukinumab 150 mg s.c. versus placebo in achieving an improvement in HAQ-DI© at Week 12.
- To evaluate secukinumab 300 mg s.c. versus placebo in achieving an improvement in the functional assessment of chronic illness therapy fatigue scale (FACIT-Fatigue©) at Week 12.
- To evaluate secukinumab 150 mg versus placebo in achieving an improvement in the FACIT-Fatigue© at Week 12.
- To evaluate secukinumab 300 mg s.c. versus placebo in achieving an improvement in the ASAS health index at Week 12.
- To evaluate secukinumab 150 mg s.c. versus placebo in achieving an improvement in the ASAS health index at Week 12.
- To evaluate secukinumab 300 mg s.c. versus placebo based on the proportion of patients achieving an ACR 20 response at Week 12.
- To evaluate secukinumab 150 mg s.c. versus placebo based on the proportion of patients achieving an ACR 20 response at Week 12.
- To evaluate the safety and tolerability of secukinumab.

[redacted]

[redacted]

3 Investigational plan

3.1 Study design

This is a 52-week, randomized, double-blind, double-dummy, placebo-controlled, multicenter study to assess the efficacy of secukinumab 150 mg or 300 mg in patients with AxPsA who have had an inadequate response to NSAIDs. The study will consist of 2 treatment periods; a placebo-controlled period from Baseline to Week 12 followed by an active treatment period from Week 12 to Week 52.

Patient eligibility will be assessed during a maximally 8-week Screening period. At Baseline, all patients whose eligibility is confirmed will be randomized in a 1:1:1 ratio to secukinumab 150 mg, secukinumab 300 mg or placebo as shown below.

At Week 12, patients randomized to placebo at Baseline will be re-randomized (1:1) to active treatment with secukinumab 150 mg or secukinumab 300 mg. See Figure 3-1 for a schematic of the study design.

Group 1: secukinumab 150 mg

Treatment Period 1

- secukinumab 150 mg (1 × 1.0 mL prefilled syringes (PFS)) + placebo (1 × 1.0 mL PFS) at Baseline, Week 1, 2, 3 and 4, then 4 weeks later at Week 8.

Treatment Period 2

- secukinumab 150 mg (1 × 1.0 mL PFS) + placebo (1 × 1.0 mL PFS) administered every 4 weeks from Week 12 to Week 52 (last dose on Week 48).

Group 2: secukinumab 300 mg

Treatment Period 1

- secukinumab 300 mg (2 × 1.0 mL PFS) administered at Baseline, Week 1, 2, 3 and 4, then 4 weeks later at Week 8.

Treatment Period 2

- secukinumab 300 mg (2 × 1.0 mL PFS) administered every 4 weeks from Week 12 to Week 52 (last dose on Week 48).

Group 3: placebo

Treatment Period 1

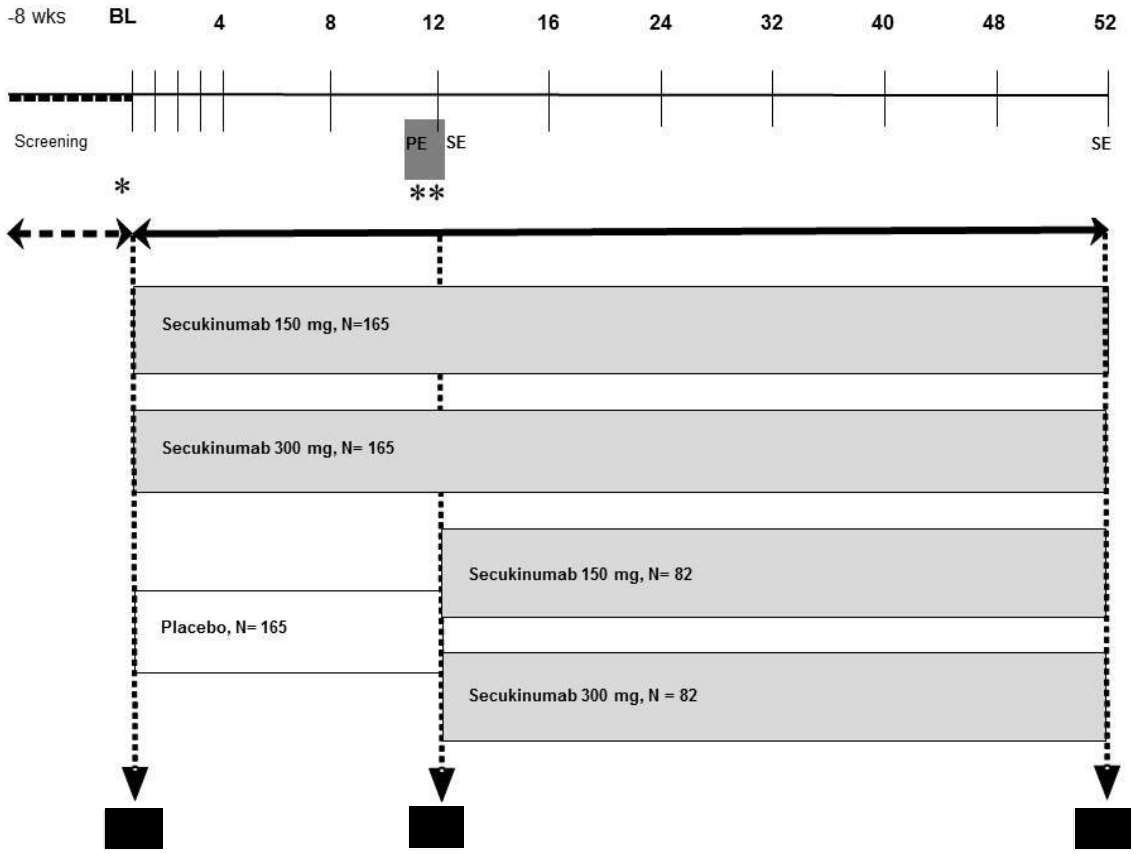
- placebo (2 × 1.0 mL PFS) administered at Baseline, Week 1, 2, 3 and 4, then 4 weeks later at Week 8.

Treatment Period 2

- secukinumab 150 mg (1 × 1.0 mL PFS) + placebo (1 × 1.0 mL PFS) administered every 4 weeks from Week 12 to Week 52 (last dose on Week 48), OR
- secukinumab 300 mg (2 × 1.0 mL PFS) administered every 4 weeks from Week 12 to Week 52 (last dose on Week 48).

[redacted]

Figure 3-1 Study design



* Randomization
** RE-randomization for placebo group
[redacted] PE = primary endpoint, SE = Secondary endpoints

During the study, patients will be required to self-administer secukinumab or placebo at the study site from Baseline to Week 12 (Treatment Period 1) and either at home or at the study center from Week 12 to end of study (last administration at Week 48) in Treatment Period 2 (see Table 6-1 and Table 6-2 for the timing of study treatment administrations).

On each treatment day, 2 s.c. injections will be administered via PFSs. This is necessary to maintain the blind since secukinumab is supplied in 1.0 mL PFSs each containing 150 mg secukinumab i.e. secukinumab 150 mg is supplied as 1 PFS and secukinumab 300 mg as 2 PFSs. Placebo to secukinumab is also available in 1.0 mL PFSs to match the active drug.

Patients will be allowed to continue background medications in accordance with the study inclusion/exclusion criteria (Section 4). In patients taking NSAIDs, the daily NSAID intake will be recorded according to ASAS recommendations (Appendix 8) up to Week 52.

[redacted]

3.2 Rationale for study design

As described in Section 1, the latest GRAPPA treatment guidelines for axial disease (Coates et al 2016) are derived from diagnostic criteria, screening, monitoring and response to therapy in AS since these data are not available for AxPsA. The effectiveness of biologics in the treatment of AxPsA has been poorly assessed and so there is an unmet need for further clinical studies of biologics in patients with AxPsA in order to evaluate their efficacy in this population, which has its own distinct radiographic features.

To address unmet medical needs, this randomized, double-blind, double-dummy, parallel-group 52-week study will evaluate the efficacy and safety of secukinumab 150 mg or 300 mg compared to placebo in patients with AxPsA. Specifically it will be performed only in patients who failed to respond to at least 2 NSAIDs over a 4 week period, which is in accordance with ASAS recommendations for the treatment of axial SpA as described in Section 1. The cut-off point (BASDAI score ≥ 4) for the definition of moderate to severe disease activity has been considered an appropriate criterion adopted from AS for axial disease in PsA. The study should provide evidence on the ability of secukinumab 150 mg or 300 mg to improve clinical [redacted] outcomes in AxPsA patients.

According to the Recommendations issued by the GRAPPA, in the absence of adequate studies in patients with AxPsA, criteria and outcome measures developed for AS have been accepted by consensus for use in AxPsA (Nash et al 2014). Therefore, the ASAS 20 improvement criteria have been chosen as primary endpoint for the present study. Week 12 was chosen to measure the primary endpoint to keep the exposure to placebo for patients in the control group to an acceptable level and still allowing patients in the verum groups to develop a stable treatment response.

The design used in this study is in alignment with Phase 3 trials of other biologics including secukinumab in this disease family and also in compliance with the European Medicines Agency (EMA) guidelines on PsA trials (EMA 2005). Treatment data up to 52 weeks is being generated to demonstrate long-term efficacy on signs, symptoms, structure, physical function and PROs, and to support the safety data in this population.

The patient population is described in more detail in Section 4.

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

The dose (150 mg and 300 mg), dose regimen (weekly from Baseline to Week 3, monthly from Week 4 to Week 52), formulation (liquid in PFSs) and route of administration (s.c.) for secukinumab used in this study are supported by the comprehensive PsA (including the pivotal Phase 3 CAIN457F2306 (Mease et al 2014) and CAIN457F2312 (Mc Innes et al 2015) studies) and AS (including the pivotal Phase 3 CAIN457F2305 and CAIN457F2310 studies (Baeten et al 2015)) clinical trial program that demonstrated the efficacy, tolerability and safety of secukinumab. Furthermore, secukinumab 150 mg and 300 mg are approved in Europe (since Nov 2015) for the treatment of PsA and AS.

[redacted]

Overall, the Phase 3 studies in PsA (CAIN457F2306 (Mease et al 2014) and CAIN457F2312 (Mc Innes et al 2015) provided evidence that secukinumab 150 mg regimen is efficacious and demonstrates clinically meaningful improvement in all clinical domains of PsA. These domains include, signs and symptoms (both for arthritic and skin symptoms), structural damage, patient reported outcomes, physical function and quality of life. [redacted]

[redacted]

Pre-filled syringes have been selected for secukinumab s.c. administration in this study as these have been successfully used in the Phase 3 clinical studies in moderate-to-severe plaque psoriasis, as well as in the completed Phase 3 clinical studies for PsA (CAIN457F2306 and CAIN457F2312), which showed the use of PFSs was safe and well tolerated.

3.4 Rationale for choice of comparator

A placebo group is included in this study up to Week 12. Due to the nature of the disease and the primary outcome measure used (to demonstrate secukinumab 300 mg is superior to placebo in the achievement of ASAS 20 score at Week 12), a placebo group is necessary to obtain reliable efficacy measurements for comparison between the active treatment groups and placebo in a controlled fashion up to 12 weeks. The continuation of the placebo group up to Week 12 is supported from an ethical standpoint. Firstly, treatment duration of the placebo group is kept to a minimum and patients can continue to be treated with a range of concomitant treatments. Secondly, the regular assessments of disease activity ensures that patients experiencing worsening of their 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. In addition, the inclusion of a placebo group is in accordance with health authority guidelines, including (EMA 2006), and the parallel-group, placebo-controlled design is in alignment with Phase 3 trials of other biologics in this therapeutic domain as outlined in EMA guidelines (EMA 2006). Furthermore, all patients randomized to the placebo group in this study will receive active treatment with secukinumab for up to 36 weeks (in Treatment Period 2).

3.4.1 Rationale for re-randomization of patients

Patients randomized to placebo at Baseline will be re-randomized to active treatment with secukinumab 150 mg or 300 mg at Week 12 irrespective of achievement of ASAS 20. Re-randomization to secukinumab will afford patients an opportunity for prevention against further structural damage in the mid to longer term. Progression of structural damage, such as progression of bone erosion, has been reported to occur in spite of achievement of clinical disease outcomes (Mease et al 2014, Mc Innes et al 2015).

[redacted]

3.6 Risks and benefits

Secukinumab is currently approved in Japan (since Dec-2014) for the treatment of PsA, as well as for the treatment of psoriasis vulgaris in adults not adequately responding to systemic therapies (except for biologics). Secukinumab is also approved in Europe (since Nov 2015) and the US (since Jan 2016) for the treatment of PsA and AS. Additionally, it is approved in Europe (since Jan 2015), the US (since Jan 2015) and Canada (since Mar 2015) for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy (US and Canada only).

As of July 2015, approximately 12 000 subjects have been enrolled in both completed and ongoing studies with secukinumab, with over 9 600 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 (RA), AS, PsA, multiple sclerosis and uveitis). Overall secukinumab was generally safe and well-tolerated.

The risk profile of secukinumab in AxPsA is informed by the safety experience from psoriasis and arthritides trials. Secukinumab has been studied most extensively in psoriasis, and side effects seen in psoriasis patients treated with secukinumab include upper respiratory tract infections (nasopharyngitis, rhinitis) (very common: in more than 1 in 10 patients); oral herpes, rhinorrhea, diarrhea and urticaria (common: in more than 1 in 100 but fewer than 1 in 10 patients); oral candidiasis, tinea pedis, neutropenia, and conjunctivitis (uncommon: in more than 1 in 1 000 but fewer than 1 in 100 patients). Additionally, worsening of Crohn's disease, in some cases serious, was seen in studies of Crohn's disease and psoriasis, in patients receiving secukinumab or placebo. Immunogenicity was low with secukinumab and did not correlate with hypersensitivity-related AEs or loss of efficacy in any of the indications studied to date.

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

4 Population

Male and female patients ≥ 18 years of age with PsA fulfilling the classification criteria for PsA (classification criteria for psoriatic arthritis (CASPAR), see Appendix 4) and who are naïve to biologic treatment. Patients must report clinical signs of spinal involvement defined by presence of inflammatory back pain (IBP) with active disease defined by BASDAI score ≥ 4, spinal pain VAS ≥ 40 (0 to 100 mm scale) and inadequate response to at least 2 NSAIDs

over 4 weeks period. Patients may continue pre-study NSAIDs, methotrexate (MTX) and corticosteroids at a stable dose from Baseline through to the end of study in accordance with the study entry criteria.

4.1 Inclusion criteria

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

1. Patients must be able to understand and communicate with the investigator and comply with the requirements of the study and must provide a written, signed and dated informed consent before any assessment is performed.
2. Male or non-pregnant, non-lactating female patients of at least 18 years of age.
3. Diagnosis of PsA classified by CASPAR criteria (Appendix 4).
4. Active spinal disease defined by BASDAI score ≥ 4 (Section 6.4.1.5).
5. Spinal pain as measured by VAS ≥ 40 at Baseline (0 to 100 mm scale) (Section 6.4.1.2).
6. Inadequate response to at least 2 NSAIDs over a 4-week period (at least).

4.2 Exclusion criteria

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

1. Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process, obtained within 3 months prior to Screening and evaluated by a qualified physician.
2. Patients taking high potency opioid analgesics (e.g. methadone, hydromorphone, morphine).
3. History of exposure to other IL-17 or IL-23 inhibitor biologic drug(s).
4. History of exposure to previous biologic DMARD(s) (TNF blockers or ustekinumab).
5. Current treatment with DMARD(s) other than MTX.
6. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization.
7. Patients regularly taking NSAIDs as part of their PsA therapy who are not on a stable dose for at least 2 weeks before study randomization.
8. Patients regularly taking systemic corticosteroids as part of their PsA therapy who are not ona stable dose ≤ 10 mg/day of prednisone or equivalent for at least 2 weeks before randomization.
9. Patients who are on MTX (≤ 25 mg/week) who are not on a stable dose for at least 4 weeks before randomization.
10. Patients on MTX who are not on folic acid supplementation at randomization.
11. Patients who are on disease modifying anti-rheumatic drug(s) (DMARD(s)) other than MTX who have not discontinued the DMARD(s) 4 weeks prior to the randomization visit, or 8 weeks prior to randomization for patients on leflunomide unless a cholestyramine washout has been performed (in which cases 4 weeks applies).
12. Active ongoing inflammatory diseases other than PsA (e.g. inflammatory bowel disease) that might confound the evaluation of the benefit of secukinumab therapy.

[redacted]

[redacted]

14. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
15. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant unless they use effective contraception during the study and longer if required by locally approved prescribing information (e.g. 20 weeks in the EU). Effective contraception is defined either as:
    a. Barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide (where available). Spermicides alone are not a barrier method of contraception and should not be used alone.

       The following methods are more effective than the barrier method and are also acceptable:
    b. Total abstinence: When this is in line with the preferred and usual lifestyle of the patient (Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception).
    c. Female sterilization: had a surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    d. Use of established oral, injected or implanted hormonal methods of contraception, intrauterine device or intrauterine system. In case of use of oral contraception women should have been stable on the same pill for a minimum of 12 weeks before taking study treatment.
    e. Male partner sterilization at least 6 months prior to Screening. For female patients on the study, the vasectomized male partner should be the sole partner for that patient.

    - Note: 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 6 months of spontaneous amenorrhea as defined by the central laboratory follicle stimulating hormone and/or estradiol levels.
16. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive or indeterminate QuantiFERON tuberculosis (TB)-Gold test (QFT) at Screening. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established then treatment according to local country guidelines must be initiated.
17. Use of any investigational drug and/or devices within 4 weeks before randomization or a period of 5 half-lives of the investigational drug, whichever is longer.
18. History of hypersensivity to the study drug or its excipient or to drugs of similar chemical classes.

[redacted]

19. Any intramuscular or intravenous (i.v.) corticosteroid treatment within 4 weeks before randomization.
20. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g. CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19).
21. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions, which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy.
22. 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.
23. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFTs), i.e. serum glutamic oxaloacetic transaminase (SGOT)/ aspartate aminotransferase (AST), serum glutamic pyruvic transaminase (SGPT)/ alanine aminotransferase (ALT), alkaline phosphatase, or serum bilirubin. The investigator will be guided by the following criteria:
    a. Any single parameter must not exceed 2 × upper limit of normal (ULN). A single parameter elevated up to and including 2 × ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out laboratory error.
    b. If the total bilirubin concentration is increased above 2 × ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed the value of 1.6 mg/dL (27 μmol/L).
24. History of renal trauma, glomerulonephritis, or patients with 1 kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6 μmol/L).
25. Screening total WBC count < 3000/μL, or platelets < 1 00 000/μL or neutrophils < 1 500/μL or hemoglobin < 8.5 g/dL (85 g/L).
26. Active systemic infections during the last 2 weeks (exception: common cold) prior to randomization.
27. Past medical history record of or current infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C prior to baseline.
28. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratosis that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).
29. Current severe progressive or uncontrolled disease, which in the judgment of the clinical investigator renders the patient unsuitable for the trial.
30. 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.
31. History or evidence of ongoing alcohol or drug abuse within the last 6 months before randomization.

[redacted]

32. Plans for administration of live vaccines during the study period or within 6 weeks preceding randomization.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Novartis will supply the following:

- Investigational treatment
  Secukinumab 150 mg provided in 1.0 ml PFS
- Placebo
  Secukinumab placebo provided in a 1.0 ml PFS

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

- AIN457 150 mg/1.0 ml/Placebo for dosing until Week 52.

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

5.1.2 Additional treatment

During this study, NSAIDs, MTX, and systemic corticosteroids are permitted as described in the sub-sections below as part of the routine medical care and will not be provided by Novartis.

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

5.1.2.1 Non-steroidal anti-inflammatory drugs

Patients who are regularly taking NSAIDs (including cyclo-oxygenase 1 (COX-1) or cyclo-oxygenase 2 (COX-2) inhibitors) at Screening should be on stable dose for at least 2 weeks before randomization to be eligible for inclusion in the study.

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

Patients are required to remain on a stable dose of NSAIDs from Baseline until Week 12. After Week 12, it is recommended that the patient continues on the same stable dose of NSAIDs until Week 52.

The dose of NSAIDs during the study must be recorded on the corresponding electronic case report form (eCRF) page.

[redacted]

5.1.2.2 Methotrexate

Patients who are taking MTX at Screening should be on a stable dose (≤ 25 mg/week) for at least 4 weeks before randomization to be eligible for inclusion in the study and apply folic acid supplement to avoid toxic effects. Patients are required to remain on a stable dose of MTX (≤ 25 mg/week) along with a folic acid supplement from Baseline until Week 12. The dose may be decreased only due to toxicity. After Week 12, it is recommended that the patient continues on the same stable dose of MTX until Week 52.

Folic acid supplementation is required so as to minimize the likelihood of MTX-associated toxicity.

The weekly dose of MTX should be taken more than 48 hours before any clinical laboratory evaluation.

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

5.1.2.3 Corticosteroids

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

Patients are required to remain on a stable dose of systemic corticosteroids up to a maximum daily dosage of 10 mg prednisone equivalent from Baseline until Week 12. After Week 12, it is recommended that the patient continues on the same stable dose of corticosteroids until Week 52.

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

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

Cortisone	1 mg
Prednisone, Prednisolone	0.2 mg
Methylprednisone, Triamcinolone	0.16 mg
Dexamethasone	0.03 mg
Fludrocortisone	0.08 mg
Deflazacort	0.24 mg
Paramethasone	0.08 mg
Hydrocortisone, cortisol	0.8 mg

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

[redacted]

5.2 Treatment arms

At Baseline, all patients whose eligibility is confirmed will be randomized in a 1:1:1 ratio to secukinumab 150 mg (Group 1), secukinumab 300 mg (Group 2) or placebo (Group 3). At Week 12, patients randomized to placebo at Baseline (i.e. Group 3) will be re-randomized in a 1:1 ratio to active treatment with secukinumab 150 mg or secukinumab 300 mg.

Group 1: secukinumab 150 mg

Treatment Period 1

- secukinumab 150 mg (1 × 1.0 mL PFS) + placebo (1 × 1.0 mL PFS) at Baseline, Week 1, 2, 3 and 4, then 4 weeks later at Week 8

Treatment Period 2

- secukinumab 150 mg (1 × 1.0 mL PFS) + placebo (1 × 1.0 mL PFS) administered every 4 weeks from Week 12 to Week 52 (last dose on Week 48)

Group 2: secukinumab 300 mg

Treatment Period 1

- secukinumab 300 mg (2 × 1.0 mL PFS) administered at Baseline, Week 1, 2, 3 and 4, then 4 weeks later at Week 8.

Treatment Period 2

- secukinumab 300 mg (2 × 1.0 mL PFS) administered every 4 weeks from Week 12 to Week 52 (last dose on Week 48)

Group 3: placebo

Treatment Period 1

- placebo (2 × 1.0 mL PFS) administered at Baseline, Week 1, 2, 3 and 4, then 4 weeks later at Week 8.

Treatment Period 2

- secukinumab 150 mg (1 × 1.0 mL PFS) + placebo (1 × 1.0 mL PFS) administered every 4 weeks from Week 12 to Week 52 (last dose on Week 48), OR
- secukinumab 300 mg (2 × 1.0 mL PFS) administered every 4 weeks from Week 12 to Week 52 (last dose on Week 48)

Patients will be allowed to continue background medications in accordance with the study inclusion/exclusion criteria.

In patients taking NSAIDs, the NSAID intake will be recorded according to ASAS recommendations up to Week 12 (see Appendix 8).

5.3 Treatment assignment and randomization

At Baseline, all eligible patients will be randomized via Interactive Response Technology (IRT) in a 1:1:1 ratio to one of the 3 treatment groups: Group 1 (secukinumab 150 mg), Group 2 (secukinumab 300 mg), or Group 3 (placebo) as described in Section 5.2. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient,

[redacted]

which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

The IRT will be programmed to allow study centers to be informed regarding which kits are for home administration versus study center administration.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the study drug(s).

At Week 12, patients in Group 3 will be re-randomized in a 1:1 ratio to secukinumab 150 mg or secukinumab 300 mg as also described in Section 5.2.

The randomization scheme for patients will be reviewed and approved by qualified randomization expert.

5.4 Treatment blinding

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

1. Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the exception of the bioanalyst.
2. The identity of the treatments will be concealed by the use of study treatments in form of PFS for s.c. injection, filled with secukinumab or placebo that are identical in appearance.

As the primary endpoint analysis will be performed at Week 12, there will be a database lock after all patients have completed Week 12 assessments (Section 9.7). A selected Novartis clinical team will be unblinded to the Week 12 results. Summary results may be shared internally and externally; however, individual unblinded patient data will not be disclosed. A final database lock will occur when all patients have completed the study.

[redacted]

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

5.5 Treating the patient

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

[redacted]

5.5.1 Patient numbering

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

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

If the patient fails to be treated for any reason, the IRT must be notified that the patient was not treated. The reason for not being treated will be entered in the CRF.

5.5.2 Dispensing the study drug

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

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the "3" treatment arms. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part (tear-off part) of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique Patient Number.

From Week 20, once the home study drug administration applies, patients will be expected to perform home drug administrations at the protocol specified time-points. For these cases, the Investigator will dispense, supported by the IRT system, an appropriate number of investigational treatment packages for home administrations. The patients will record details including the date of administration at home in a self-administration log and will return the used medication (if in compliance with local rules and guidelines) and medication packaging, together with the self-administration log, at their next visit to the study center. Patients will be asked to return all unused study drug and packaging at each scheduled study visit and by the very latest at the end of the study.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

The study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study drugs 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 following Novartis processes for instance to the respective Novartis country pharma organization (CPO) Quality Assurance.

The PFSs sealed in their outer box must be stored in a locked refrigerator between 2°C and 8°C (36°F and 46°F) and must be carefully controlled in accordance with regulations governing investigational medicinal products, local regulations and in accordance with

[redacted]

instructions from the Novartis Drug Supply Management or Novartis Drug Supply Chain or corresponding service providers. The study drug should be protected from light and must not be frozen.

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

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused study treatment and packaging latest 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 drug, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis associate or sponsor designee or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Patients will self-administer secukinumab 150 mg (1 × 150 mg PFS and 1 × placebo PFS), secukinumab 300 mg (2 × 150 mg PFSs) or placebo (2 × placebo PFS) by s.c. injection of 1 mL each. The dosing frequency will be either weekly or every 4 weeks in accordance with the administration schedule (Table 6-1 and Table 6-2). The last dose administration will occur at Week 48.

Patients will receive instructions and training from study center staff on how to self-administer the study drug. The injections up to Week 16 and the subsequent ones occurring during a visit will be done by the patient (or caregiver) at the study center, under the supervision of the Investigator or study staff (i.e. at Baseline, Weeks 1, 2, 3, 4, and 8 during Treatment Period 1; and Week 12, 16, 24, 32, 40 and 48 during Treatment Period 2).

The patient will be instructed on the use of secukinumab via review of instructions for use (IFU) for secukinumab PFSs (PFS-IFU). At subsequent visits, the Investigator/qualified study center staff will observe the self-administration of secukinumab at the clinic. The injections not occurring during a study center visit will be done by eligible patients (or caregiver) at their home (Week 20, 28, 36 and 44 during Treatment Period 2).

All dosages prescribed and dispensed to the patient during the study must be recorded in the eCRF.

The patient will document all doses and dates of self-administration at home in a self-administration log. Patients are required to return the self-administration log at every visit to the study center.

[redacted]

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

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

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

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

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments are not permitted. Study drug interruption should be avoided with the following exceptions:

Study drug interruption is only permitted if, in the opinion of the investigator, a patient 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.

These changes must be recorded on the appropriate CRF page.

5.5.6 Rescue medication

Please refer to Section 5.1.2 for details of the additional treatments (MTX, NSAIDs, and corticosteroids) permitted for use alongside secukinumab in this study.

Rescue medication is defined as any new therapeutic intervention or a significant change to ongoing therapy made because a patient is experiencing either no benefit from participation in the trial or a worsening/exacerbation of their disease. Rescue medication must not be used before completion of Week 52 assessments. Please see Section 5.5.7 and Section 5.5.8 for details on concomitant and prohibited medication for this study.

If prohibited treatments (as described in Section 5.5.8) are administered prior to completion of the Week 52 visit, patients will be discontinued from the study treatment but can continue with the study visit assessments until at least Week 12 (i.e. time of primary analysis).

Use of rescue medication must be recorded on the Concomitant medications in the CRF.

[redacted]

5.5.7 Concomitant medication

Please refer to Section 5.1.2 for details of the additional treatments (MTX, NSAIDs, and corticosteroids) permitted for use alongside secukinumab in this study.

All patients should have had adequate therapeutic trial of (or inadequate therapeutic effect with) at least two NSAIDs; defined as at least two NSAIDs over a 4-week period in a total at maximum recommended dose unless contraindicated (van der Heijde et al 2011) and keep NSAID treatment on a stable dose during the study.

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

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-2 is NOT allowed after the start of the washout period. Live vaccines should not be given until 12 weeks after last study treatment administration.

Table 5-2 Prohibited medication

Prohibited medication	Washout period (before randomization)
Biological immunomodulating agents	Never
Unstable dose of MTX	4 weeks
Other DMARD (except MTX)	4 weeks
Leflunomide	8 weeks
Leflunomide with cholestyramine washout	4 weeks
Unstable dose of NSAIDs (COX1 or COX2 inhibitors)	2 weeks
Analgesics other than NSAIDs, paracetamol/acetaminophen and low strength opioids PRN	2 weeks
Systemic corticosteroids > 10 mg prednisone equivalent*	2 weeks
Unstable dose of systemic corticosteroids ≤ 10 mg prednisone equivalent	2 weeks
Intra-articular injections	4 weeks
Intramuscular or intravenous corticosteroid treatment	4 weeks
Any investigational treatment or participation in any interventional Trial	4 weeks or 5 half-lives (whichever is longer)
Live vaccines	6 weeks

Abbreviations: COX = cyclo-oxygenase, DMARD = disease modifying anti-rheumatic drug, MTX = methotrexate, NSAIDs = non-steroidal anti-inflammatory drugs, PRN = pro re nata (as needed);
* See details about corticosteroid management in Section 5.1.2.3.

[redacted]

5.5.9 Emergency breaking of assigned treatment code

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

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number CAIN457F3302, study drug name if available, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case an emergency unblinding is required at a time when the investigator and backup are unavailable.

Study drug must be discontinued after emergency unblinding.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

Study completion is defined as all patients who have been enrolled at Baseline and completed the study as described in the protocol.

The Investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

Patients who successfully complete the current study may be given the opportunity to enter an extension study. If an extension study is agreed on, it will be described in a separate extension study protocol.

5.6.2 Discontinuation of study treatment

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

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

Study treatment must be discontinued if the investigator determines that continuation of study treatment would result in a significant safety risk for a patient.

The following circumstances require study treatment discontinuation:

- Withdrawal of informed consent

[redacted]

- Emergence of the following AEs:
  - Any severe AE or SAE that is not compatible with administration of study medication, including AEs that require treatment with an unacceptable concomitant 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.
  - Severe hypersensitivity reaction or anaphylactic reaction.
- Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the patient at a safety risk for continuation in the study (A general guidance on clinically notable laboratory values is provided in Appendix 1).
- Pregnancy.
- Use of any biologic immunomodulating agent except secukinumab.
- Any protocol deviation that results in a significant risk to the patient's safety.

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

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

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

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

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

Patients who prematurely discontinue the study should return and complete assessments associated with Week 52 visit (4 weeks after the last study treatment, see Table 6-1) and any Adverse Events that are treatment emergent should be reported until 12 weeks after last study treatment. The final visit should be performed before any new treatment is initiated.

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

5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- 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, and

[redacted]

- Does not allow analysis of already obtained biologic material.

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

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

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in Table 6-1.

5.6.4 Loss to follow-up

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

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

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

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

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

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

[redacted]

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

No study assessment will be performed unless patients sign the ICF. Once patient signs the ICF, he will be screened for eligibility criteria. Screening will be flexible in terms of the time required to washout prior antirheumatic and other medications and will have a duration of up to 8 weeks.

During the Screening Visit, initial assessments will be performed as outlined in Table 6-1. The duration of the washout period will be determined at the Screening Visit. Note: All patients evaluated at Screening (Visit 1) for eligibility should not be screen failed on the basis of a medication requiring washout, unless the patient will be unable to complete the washout in the appropriate time frame before randomization. Patients should be seen for all visits to perform the scheduled assessments on the designated day, or as close to is as possible, i.e., not exceeding recommended visit window outlined in Table 6-1 and Table 6-2.

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

[redacted]

Table 6-1 Assessment schedule

	Scr	Bsl	Double-blind placebo-controlled period (last dose at Week 8)						Double-blind active treatment period (last dose at Week 48)						USV**	Comments
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 EOS/ PPD***		* Patients who prematurely discontinue during the treatment period should return for assessments associated with the Week 52 visit (i.e. 4 weeks after the last study treatment). **Unscheduled visits – assessments at the discretion of the investigator
Week	**-8**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**52**		
Recommended visit window (days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 2**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**		
Obtain informed consent	X															
Inclusion & exclusion criteria	X	X														
Randomization via IRT		X						X#								# At Visit 8, all patients receiving placebo will be re-randomized to receive 150 mg secukinumab or 300 mg secukinumab in a 1:1 ratio
IRT contact such as for registration or drug supply including home administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Study drug administration at the study center		X	X	X	X	X	X	X	X	X	X	X	X			Please refer Table 6-2 to for timing of home administrations.
Demography	X															
Relevant medical history/current medical condition	X	X														
Wash out evaluations/instructions	S															
Smoking history		X														

[redacted]

	Scr	Bsl	Double-blind placebo-controlled period (last dose at Week 8)						Double-blind active treatment period (last dose at Week 48)						USV**	Comments
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 EOS/ PPD***		* Patients who prematurely discontinue during the treatment period should return for assessments associated with the Week 52 visit (i.e. 4 weeks after the last study treatment). **Unscheduled visits – assessments at the discretion of the investigator
Week	**-8**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**52**		
Recommended visit window (days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 2**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**		
Cardiovascular medical history		X														
AxPsA medical history and previous therapies	X	X														
CASPAR criteria	X														X	
Physical examination	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	These assessments are source documentation only and will not be entered into the CRF.
Height	X														X	
Weight	X	X						X						X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
QuantiFERON TB-Gold test	X														X	
Chest X-ray/MRI (for study inclusion)	S														S	If patients do not have a chest X-ray available within 3 months of Screening, an X-ray should be performed after it is certain the patient meets inclusion/exclusion criteria in order to minimize unnecessary exposure to X-ray radiation. In some sites selected by Novartis, the X-ray assessment may be replaced by chest MRI assessment.
Safety laboratory (clinical chemistry, hematology, urinalysis)	X	X						X		X		X		X	X	Dipsticks will be provided by the central laboratory to the sites for local urinalysis assessments Samples must be obtained fasting.

[redacted]

	Scr	Bsl	Double-blind placebo-controlled period (last dose at Week 8)						Double-blind active treatment period (last dose at Week 48)						USV**	Comments
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 EOS/ PPD***		* Patients who prematurely discontinue during the treatment period should return for assessments associated with the Week 52 visit (i.e. 4 weeks after the last study treatment). **Unscheduled visits – assessments at the discretion of the investigator
Week	**-8**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**52**		
Recommended visit window (days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 2**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**		
[redacted]																
Lipid lab panel		X						X						X	X	Samples must be obtained fasting.
Cardiovascular lab panel		X						X						X	X	
Electrocardiogram		X						X						X	X	
Serum pregnancy test	X														X	
Urine pregnancy test		X				X		X	X		X			X	X	
Hepatitis B, C or HIV serology (only in countries where required)	S															Hepatitis B and/or hepatitis C and/or HIV serology testing to be performed during screening period only if required as per local medical practice or local regulations prior to initiation of therapy. These assessments will be documented in source records only and will not be entered into the eCRF
BASFI		X				X	X	X	X	X	X	X	X	X	X	
BASDAI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Spinal pain VAS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient's global assessment of disease activity (VAS)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient's assessment of PsA pain (VAS)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

	Scr	Bsl	Double-blind placebo-controlled period (last dose at Week 8)						Double-blind active treatment period (last dose at Week 48)						USV**	Comments
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 EOS/ PPD***		* Patients who prematurely discontinue during the treatment period should return for assessments associated with the Week 52 visit (i.e. 4 weeks after the last study treatment). **Unscheduled visits – assessments at the discretion of the investigator
Week	**-8**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**52**		
Recommended visit window (days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 2**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**		
Physician's global assessment of disease activity (VAS)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
[redacted]																
SPARCC enthesitis index		X				X	X	X	X	X	X	X	X	X	X	
78 tender joint count		X				X	X	X	X	X	X	X	X	X	X	
76 swollen joint count		X				X	X	X	X	X	X	X	X	X	X	
[redacted]																
FACIT-Fatigue©		X				X	X	X	X	X				X	X	
HAQ-DI©		X				X	X	X	X	X	X	X	X	X	X	
ASAS health index		X				X	X	X	X	X				X	X	
Prior/concomitant medication/non-drug therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AEs/SAEs (including injection site reactions)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	AEs/SAEs occurring after the patient has signed the informed consent must be captured on the appropriate eCRF page. Any AEs that are treatment emergent should be reported until 12 weeks after last study treatment.
Check self-administration log										S	S	S	S	S	S	Patients must return the self-administration log along with all dispensed PFS and drug packaging at every visit, if applicable.

[redacted]

	Scr	Bsl	Double-blind placebo-controlled period (last dose at Week 8)						Double-blind active treatment period (last dose at Week 48)						USV**	Comments
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 EOS/ PPD***		* Patients who prematurely discontinue during the treatment period should return for assessments associated with the Week 52 visit (i.e. 4 weeks after the last study treatment). **Unscheduled visits – assessments at the discretion of the investigator
Week	**-8**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**52**		
Recommended visit window (days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 2**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**		
Treatment completion form														X		

AE = adverse event, ASAS = assessment of spondyloarthritis international society, AxPsA = axial psoriatic arthritis (i.e. psoriatic arthritis with axial involvement), BASDAI = Bath ankylosing spondylitis disease activity index, BASFI = Bath ankylosing spondylitis functional index, CASPAR = classification criteria for psoriatic arthritis, FACIT-Fatigue© = functional assessment of chronic illness therapy fatigue scale, HAQ-DI© = health assessment questionnaire – disability index, [redacted], IRT = interactive response technology, [redacted], PFS = prefilled syringe, PPD = premature patient discontinuation, SAE = serious adverse event, SPARCC = Spondyloarthritis Research Consortium of Canada, VAS = visual analog scale

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

[redacted]

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

Study Visit	**8**	**9**		**10**		**11**		**12**		**13**	**14**
Week	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Recommended visit window (days)	± 2	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5
Study drug administration											
All Groups	**S**	**S**	**H**	**S**	**H**	**S**	**H**	**S**	**H**	**S**	

Abbreviations: H = home administration; S = administration at study center

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next period will have the study completion page for the Screening period, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

All patients who have signed informed consent but discontinue prior to first intake of study drug on Day 0 (Baseline Visit) are considered to be screen failures. If a patient discontinues prior to or at Day 0, the reason for screen failure will be entered on the appropriate eCRF page.

For details on completing the eCRF please refer to the CRF completion guideline. In brief the Screening information such as the visit date, information on demography, informed consent, and the inclusion/exclusion criteria, must be completed. The AE eCRF should be completed for any AEs that occurred during the Screening period. Information on withdrawal of consent must be completed if consent has been withdrawn during the Screening period. The Death eCRF should be completed in the case of death during the Screening period.

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

At the discretion of Investigators, abnormal test findings if judged clinically significant should be recorded after informed consent signature on the AE eCRF page.

6.2 Patient demographics/other baseline characteristics

All Baseline assessments should be performed prior to first study drug administration. These may occur during the Screening period or at the Baseline Visit depending on the assessment (Table 6-1).

6.2.1 Demographic data

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

[redacted]

6.2.2 Baseline characteristics

6.2.2.1 Psoriatic arthritis history

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

- Date of first diagnosis of AxPsA prior to the Baseline Visit (by a rheumatologist)
- Date of first signs and symptoms of AxPsA
- Previous treatments of AxPsA and the reason for discontinuation.

6.2.2.2 Smoking history

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

6.2.2.3 Co-morbidities – cardiovascular medical history

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

6.2.2.4 Relevant medical history/concurrent medical conditions

Relevant medical history and current medical conditions (not including AxPsA) present prior to signing the ICF will be recorded in the Medical History eCRF. Whenever possible, diagnoses and not symptoms will be recorded.

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

6.2.2.5 Prior and concomitant medications

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

6.2.2.6 Chest X-ray

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

6.2.3 Other baseline characteristics

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

[redacted]

- Vital signs; hematology, clinical chemistry and urine laboratory tests; fasting laboratory tests (glucose, lipid panel, [redacted]); cardiovascular panel; electrocardiogram (ECG); physical examination, height, weight; TB status (Section 6.5.4). For women of child-bearing potential, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at Baseline.
- Baseline efficacy assessments (see Section 6.4): ASAS components (patient's global assessment of disease activity, patient's assessment of IBP intensity VAS, BASDAI and Bath ankylosing spondylitis functional index (BASFI)); SPARCC; ACR components (78 tender joint count (TJC), 76 swollen joint count (SJC), physician's global assessment of disease activity, patient's assessment of PsA pain; other components already captured under ASAS components); [redacted]
- Additional PRO assessments not covered under efficacy assessments (see Section 6.6): HAQ-DI©, Facit-Fatigue© and ASAS health index.

Whenever possible, diagnoses and not symptoms will be recorded.

6.3 Treatment exposure and compliance

All doses of study drug administered will be recorded in the eCRF. Patient compliance to the study drug should be assessed by qualified study center personnel at each study visit using the study kits and documentation regarding study drug dispensation and administration.

Compliance will also be assessed continuously during the conduct of the study by Novartis study personnel using medication kits and corresponding documentation. Study drug doses and corresponding dates of self-administration at home should be documented in a self-administration log. Patients are required to return the self-administration log as well as all dispensed study drug at every visit back to the study center for a compliance check.

6.4 Efficacy

All efficacy assessments should be performed prior to administration of the study drug.

- Assessment of spondyloarthritis international society (ASAS) responses
- Bath ankylosing spondylitis disease activity index (BASDAI)
- Bank ankylosing spondylitis functional index (BASFI)
- Spinal pain (VAS)
- Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index
- American College of Rheumatology 20 (ACR 20)

[redacted]

6.4.1 Assessment of spondyloarthritis international society

The ASAS response criteria are presented in full in Appendix 5. The ASAS response measures consisted 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 (Section 6.4.1.1)
2. Patient's assessment of IBP, represented by either total or nocturnal pain scores, both measured on a VAS scale (Section 6.4.1.2).
3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS scale (Section 6.4.1.6).
4. Morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI regarding morning stiffness as measured by VAS scale (Section 6.4.1.5).

6.4.1.1 Patient's global assessment of disease activity

The patient's global assessment of disease activity will be performed using 100 mm VAS ranging from "very good" to "very poor", after the question "*Considering all the ways psoriatic arthritis affects you, please indicate with a vertical mark (|) through the horizontal line how well you are doing today*".

6.4.1.2 Patient's assessment of inflammatory back pain intensity (VAS)

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

6.4.1.3 ASAS response criteria (ASAS 20)

The ASAS Response Criteria (ASAS 20) was defined as an improvement of ≥ 20% and ≥ 1 unit on a scale of 10 in at least 3 of the 4 main domains and no worsening of ≥ 20% and ≥ 1 unit on a scale of 10 in the remaining domain.

6.4.1.4 ASAS response criteria (ASAS 40)

The ASAS 40 response was defined as an improvement of ≥ 40% and ≥ 2 units on a scale of 10 in at least 3 of the 4 main domains and no worsening at all in the remaining domain.

6.4.1.5 Bath ankylosing spondylitis disease activity index

The BASDAI is the gold standard for measuring and evaluating disease activity in AS (Section 17.2). 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

[redacted]

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. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score. Scores of 4 or greater suggest suboptimal control of disease, and patients with scores of 4 or greater are usually good candidates for either a change in their medical therapy or for enrollment in clinical trials evaluating new drug therapies directed at AS. BASDAI is a quick and simple index taking between 30 secs and 2 mins to complete.

6.4.1.6 Bath ankylosing spondylitis functional index

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those patients with AS. The 10 questions were chosen with a major input from patients with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the patient's ability to cope with everyday life. A 0 through 10 scale (captured as a continuous VAS) is used to answer the questions. The mean of the 0 scales gives the BASFI score a value of between 0 and 10.

6.4.2 Spondyloarthritis research consortium of Canada – enthesitis index

The SPARCC (Maksymowych et al 2009) enthesitis index focuses on the clinical evaluation and validation of the 16 sites shown in Table 6-3. SPARCC assessments will be performed as indicated in the schedule of assessments (Table 6-1).

Table 6-3 Entheses sites comprising the total spondyloarthritis research consortium of Canada enthesitis index

Greater trochanter	R/L
Quadriceps tendon insertion into the patella	R/L
Patellar ligament insertion into the patella and tibial tuberosity	R/L
Achilles tendon insertion	R/L
Plantar fascia insertion	R/L
Medial epicondyles	R/L
Lateral epicondyles	R/L
Supraspinatus insertion	R/L

Abbreviations: R = right, L = left

Note: Tenderness at each site is quantified on a dichotomous basis: 0=non-tender and 1=tender. Range of scores: 0 to 16

[redacted]

6.4.3 American college of rheumatology response

The ACR response (Appendix 9) will be used to determine efficacy (Felson et al 1995). A patient is defined as e.g. an ACR 20 responder if, and only if, the following 3 conditions hold:

- Patient has a ≥ 20% improvement in the number of tender joints (based on 78 joints) (Section 6.4.3.1).
- Patient has a ≥ 20% improvement in the number of swollen joints (based on 76 joints) (Section 6.4.3.1).
- Patient has a ≥ 20% improvement in 3 of the following 5 domains:
  1. Patient's global assessment of disease activity (measured on a VAS scale, 0-100) (Section 6.4.1.1).
  2. Physician's global assessment of disease activity (measured on a VAS scale, 0-100) (Section 6.4.3.2).
  3. Patient's assessment of PsA pain (measured on a VAS scale, 0-100) (Section 6.4.3.3)
  4. HAQ-DI© score (Section 6.6.1.1).
  5. Acute phase reactant [redacted]

An ACR 50 response is defined as a 50% improvement in at least 3 of the 5 measures and a 50% improvement in the SJC and TJC.

An ACR 70 response is defined as a 70% improvement in at least 3 of the 5 measures and a 70% improvement in the SJC and TJC.

The ACR response is to be assessed at the visits/time points shown for the components of the ACR in Table 6-1.

6.4.3.1 Tender 78 joint count and swollen 76 joint count

Joint counts will be performed by an independent assessor. Whenever possible, the same evaluator should perform these assessments at all visits.

The 78 joints to be assessed for tenderness include the following:

- 2 temporomandibular, 2 sternoclavicular, 2 acromioclavicular joints
- 2 shoulders, 2 elbows, 2 wrists
- 2 first carpometacarpal, 10 metacarpophalangeal, 10 proximal interphalangeal, and 8 distal interphalangeal joints of the hands
- 2 hips, 2 knees, 2 talo-tibial, 2 mid-tarsal, 10 metatarsophalangeal, and 10 proximal interphalangeal and 8 distal interphalangeal joints of the feet.

All of the above (except for the hips) will be assessed for swelling. Joint tenderness and swelling are to be graded present (1) or absent (0).

Synovial fluid and/or soft tissue swelling but not bony overgrowth represents a positive result for SJC.

Dactylitis of a digit in the foot or hand counts as 1 tender and swollen joint.

[redacted]

Data is recorded for tender and swollen joints (right or left side), i.e. a box (no, yes or not applicable) needs to be ticked for all joints. The total number of tender and swollen joints (right and left) will be automatically calculated in the eCRF.

6.4.3.2 Physician's global assessment of disease activity

The physician's global assessment of disease activity will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question *"Considering all the ways the disease affects your patient, draw a line on the scale for how well his or her condition is today"*. To enhance objectivity, the physician must not be aware of the specific patient's global assessment of disease activity, when performing his own assessment on that patient.

6.4.3.3 Patient's assessment of PsA pain

The patient's assessment of PsA pain will be performed using a 100 mm VAS ranging from no pain to unbearable pain after the question "*Please indicate with a vertical mark (|) through the horizontal line the most pain you had from your psoriatic arthritis today*."

[redacted]

6.4.7 Appropriateness of efficacy assessments

Evaluation tools used in this study have been used previously in clinical trials for PsA and AS. Evaluation of disease severity based on clinical scoring (ASAS) is commonly used in the studied indication.

[redacted]

[redacted]

6.5 Safety

All safety assessments should be performed as indicated in Table 6-1 prior to study drug administration.

- Evaluation of AE/SAEs (including injection site reactions)
- Physical examination
- Vital signs
- Height and weight
- QuantiFERON TB-Gold test
- Electrocardiogram
- Laboratory evaluations (hematology, clinical chemistry, urinalysis, lipid panel, cardiovascular panel)
- Pregnancy and assessment of fertility
- Tolerability of secukinumab

Appropriate safety assessments (e.g. evaluation of AEs and SAEs including injection site reactions) should be repeated after the dose is administered.

6.5.1 Physical examination

A complete physical examination will be performed that will include the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular system 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 which meet the definition of an AE must be recorded in the AE eCRF.

6.5.2 Vital signs

Vital signs (including blood pressure and pulse measurements) will be assessed after the patient has been sitting for 5 minutes, with back supported and both feet placed on the floor, systolic and diastolic **blood pressure will be measured thrice** (measurements separated by 1 to 2 minutes) using a validated device with an appropriately sized cuff and each blood pressure measurement will be recorded in the source (Mancia et al 2007). In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. If possible, assessments should be performed by the same study site staff member throughout the study.

[redacted]

Normal blood pressure will be defined as a systolic pressure of 90 to < 120 mmHg, and a diastolic blood pressure of 60 to < 80 mmHg under the measurement conditions outlined above. Notable blood pressure will be hypertension (systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg) or hypotension (systolic blood pressure of < 90 mmHg and/or a diastolic blood pressure of < 60 mmHg). A blood pressure indicative of prehypertension (systolic blood pressure of 120 to < 140 mmHg and/or diastolic blood pressure of 80 to < 90 mmHg) will not be regarded as notable (Chobanian et al 2003).

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

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

6.5.3 Height and weight

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

6.5.4 QuantiFERON TB-Gold test

A QuantiFERON TB-Gold test must be performed at the Screening Visit and the results must be known prior to randomization to determine the patient's eligibility for the trial. The test will be used to screen the patient population for latent tuberculosis infection. The test will be analyzed by the central laboratory. Details on the collection, processing and shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual.

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

6.5.5 Laboratory evaluations

A central laboratory will be used for analysis of all specimens listed below (except urinalysis). Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual. For the identification of clinically notable values, see Appendix 1.

All patients with laboratory tests containing clinically significant abnormal values are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

6.5.5.1 Hematology

Hematology sampling includes hemoglobin, platelet, red blood cell, WBC and differential WBC counts will be measured at scheduled visits.

[redacted]

6.5.5.2 Clinical chemistry

Serum chemistries includes glucose, urea, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), gamma glutamyl transferase (GGT), alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorous, total protein, albumin, and uric acid.

6.5.5.3 Urinalysis

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

6.5.5.4 Lipid panel

A lipid profile including high density lipoprotein, low density lipoprotein, cholesterol and triglycerides will be measured from a fasting blood sample.

6.5.5.5 Cardiovascular panel

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

6.5.6 Electrocardiogram

A standard 12-lead ECG will be performed as indicated in the schedule of assessments (Table 6-1). The Investigator/qualified site staff must review and initial the tracing. The tracing must then be stored with the patient's source documents. If the ECG findings are clinically relevant and would prevent the patient from participating in the study (taking into account the patient's overall status as well as the medication profile), the patient should be recorded as a screen failure, should NOT be enrolled and should not receive treatment. All ECGs will be independently reviewed by a central reader. Instructions for the collection and transmission of the ECGs to the independent reviewer will be provided in the ECG Investigator manual. Although there is no exclusion criterion specifically based on the ECG, the Baseline ECG performed at the Baseline Visit must be reviewed for major abnormalities before dosing at the Baseline Visit.

6.5.7 Pregnancy and assessments of fertility

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

A serum β-hCG test will be performed in all women at Visit 1 (Screening). All women who are not surgically sterile at Screening will have local urine pregnancy tests as indicated in Table 6-1. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If positive, the patient must be discontinued from the trial.

[redacted]

6.5.8 Appropriateness of safety measurements

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

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

6.6 Other assessments

6.6.1 Patient reported outcomes

The impact of secukinumab on various aspects of patients' health will be assessed using the following measures:

- Health assessment questionnaire – disability index (HAQ-DI©)
- Functional assessment of chronic illness therapy fatigue scale (FACIT-Fatigue©)
- ASAS health index

The BASDAI, a PRO assessing disease activity, and BASFI, a PRO assessing functional limitation, which are part of ASAS are described under efficacy assessments in Section 6.4.1.

6.6.1.1 Health assessment questionnaire – disability index (HAQ-DI©)

The HAQ-DI© was developed by Stanford University and is one of the most widely used measures to assess the long-term influence of chronic disease on a patient's level of functional ability and activity restriction. The disability assessment component of the HAQ, the HAQ-DI©, assesses a patient's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning including dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The "stem" of each item asks over the past week "Are you able to …" perform a particular task. Each item is scored on a 4-point scale from 0 to 3, representing normal (normal, no difficulty [0]), some difficulty (1), much difficulty (2), and unable to do (3).

The purpose of the HAQ-DI© in this study is to assess the functional ability of patients with PsA.

6.6.1.2 Functional assessment of chronic illness therapy fatigue scale (FACIT-Fatigue©)

The FACIT-Fatigue© is a 13-item questionnaire (Cella et al 1993 and Yellen et al 1997) that assesses self- reported fatigue and its impact upon daily activities and function.

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

[redacted]

6.6.1.3 ASAS health index

The ASAS health index is a disease-specific questionnaire that was developed based on the comprehensive international classification of functioning, disability and health (ICF) Core Set for AS (Kiltz et al 2014). The ASAS health index is the first disease-specific PRO measure aimed at measurement of overall functioning and health based on the ICF in patients with SpA. The ASAS health index is a linear composite measure and contains 17 items (dichotomous response option: "I agree" and "I do not agree"), which cover most of the ICF core set, as presented in Table 6-4.

Table 6-4 Items of the ASAS health index

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

Source: Kiltz et al 2014

7 Safety monitoring

7.1 Adverse events

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

In addition, all reports of intentional misuse and abuse of the product are also considered an AE irrespective if a clinical event has occurred.

[redacted]

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

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from Baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying AEs. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade
    - mild: usually transient in nature and generally not interfering with normal activities
    - moderate: sufficiently discomforting to interfere with normal activities
    - severe: prevents normal activities
- its relationship to the
- study treatment (no/yes), or
- other treatment (no/yes) or
- both or indistinguishable
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a SAE (see Section 7.2 for definition of SAE)
- action taken regarding study treatment

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

- no action taken (e.g. further observation only)
- study treatment dosage adjusted/temporarily interrupted
- study treatment permanently discontinued due to this AE
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

[redacted]

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

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

The investigator must also instruct each patient to report any new AE (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. Any Adverse Events that are treatment emergent should be reported until 12 weeks after last study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

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

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

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

[redacted]

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

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

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

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 12 weeks (84 days) after last administered dose of study treatment or 30 days after the patient has stopped study participation (whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded on the paper SAE Report Form. The investigator must assess the relationship to each specific component of study treatment (if study treatment consists of several components) complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department or via an equal electronic sponsor system (in case applicable as per local processes and regulations). The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the CRF documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

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

[redacted]

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 Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an IN to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

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

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

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Appendix 2.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation.

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

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

For the liver events:

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

[redacted]

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

7.4 Renal safety monitoring

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

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

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

7.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE.

Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-1 Treatment error types

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

DAR: drug administration record

[redacted]

7.6 Pregnancy reporting

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

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

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

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and good clinical practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, 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 and identify risks and trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

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

[redacted]

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic CRFs using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Web based software will be used: no installation procedure will be needed. Each site will be authorized by the Administrator to access into the eCRF. Each investigator site qualified personnel would be allowed to access to the eCRF by means of a 'login mask' requiring User ID and Password and it would be possible to read, modify and update only the information he/she had previously reported. All pages should report site code and patient code. On-line validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the investigator will receive a CD-ROM with patient data for archiving at the investigational site.

8.3 Database management and quality control

The CRO working on behalf of Novartis reviews the data entered into the CRFs by investigational staff for completeness and accuracy and instructs the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to the CRO working on behalf of Novartis that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

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

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

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

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

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

[redacted]

8.4 Data monitoring committee

Not required.

8.5 Adjudication committee

Not required.

9 Data analysis

Summary statistics for continuous variables will generally include the number of patients (N), minimum, lower quartile, mean, median, upper quartile, and maximum. For categorical or binary variables, the number and percent of patients in each category will be presented. P-values presented will be 2-sided unless otherwise specified.

Inferential efficacy comparisons with placebo will be done on the first 12 weeks of treatment.

Data analyses will be presented by treatment group. Efficacy and safety data for the placebo-controlled period (or the entire treatment period as appropriate) will be presented by the following 3 treatment groups. Patients may be included in more than 1 treatment group for some analyses (e.g. exposure-adjusted AEs over the entire treatment period).

Patients will be randomized to secukinumab 150 mg (Group 1), secukinumab 300 mg (Group 2) or placebo (Group 3) as described in Section 5.2 and Section 5.3.

Note that the treatment groups above for a patient may differ depending on the time period of the analysis and whether one assesses the patient for efficacy or safety (see Section 9.1 for details).

The analysis will be conducted on all patient data at Week 12 and at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

The following analysis sets will be used in this trial:

Randomized set: The randomized set will be defined as all patients who were randomized.

Unless otherwise specified, mis-randomized patients (mis-randomized in IRT) will be excluded from the randomized set.

Mis-randomized patients are defined as those patients 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 patients are treated as screen failures.

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

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

[redacted]

Per-protocol set: This set includes all patients who completed the study without a major protocol deviation.

9.2 Patient demographics and other baseline characteristics

9.2.1 Demographics and baseline characteristics

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

Demographic and baseline disease characteristics will be summarized for the variables listed in Section 6.2.

9.2.2 Medical history

Any significant prior or active medical condition at the time of signing informed consent will be coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term.

Summaries for cardiovascular and psoriasis specific medical history will also be provided.

9.3 Treatments

9.3.1 Study treatment

The analysis of study treatment data will be based on the Safety set. The number of active and placebo injections received will be presented by treatment group up to Week 52.

The duration of exposure to study treatment will also be summarized by treatment group. In addition, the number and percentage of patients with cumulative exposure levels (e.g. any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, ≥ 8 weeks, etc.) will be presented.

Duration of exposure is defined as the time from first dose of study treatment to the time of treatment switch (for patients who switch treatment) or end of treatment period. For patients who discontinue this will be the last visit in the corresponding treatment period.

9.3.2 Prior and concomitant medication

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

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

Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group.

[redacted]

Tables will show the overall number and percentage of patients receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

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

The number and percentage of patients receiving prior and concomitant PsA 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 PsA therapies previously.

9.4 Analysis of the primary and key secondary variable(s)

Details of the testing strategy including primary, key secondary and secondary endpoints are provided in Section 9.4.1 and Section 9.5.1 and details are provided in the statistical analysis plan.

9.4.1 Variable

The primary and key secondary efficacy variable is the proportion of patients with a response to treatment as assessed by the ASAS 20 criteria at Week 12.

The analysis of both the primary and key secondary variables will be based on the FAS.

9.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypothesis for ASAS 20 being tested is that there is no difference in the proportion of patients fulfilling the ASAS 20 criteria at Week 12 in the secukinumab group versus placebo group.

Let p_0 denotes the proportion of ASAS 20 responders at Week 12 for placebo group and p_j denotes the proportion in secukinumab (150 mg or 300 mg) treatment group.

- 1 corresponds to secukinumab 300 mg and
- 2 corresponds to secukinumab 150 mg

In statistical terms, the following hypothesis will be tested for primary objective:

H_1: $p_1 = p_0$, versus H_{A1}: $p_1 \neq p_0$

If primary objective is met, the following hypothesis will be tested for the key secondary objective:

H_2: $p_2 = p_0$, versus H_{A2}: $p_2 \neq p_0$,

In other words,

H_1: Secukinumab (300 mg) treatment group is not different to placebo group with respect to ASAS 20 response at Week 12

H_2: Secukinumab (150 mg) treatment group is not different to placebo group with respect to ASAS 20 response at Week 12

[redacted]

The primary and key secondary analyses will be conducted via logistic regression with treatment and concomitant MTX intake status as factors. Odds ratios, 95% confidence interval (CI) and p-values will be presented comparing each secukinumab group to placebo.

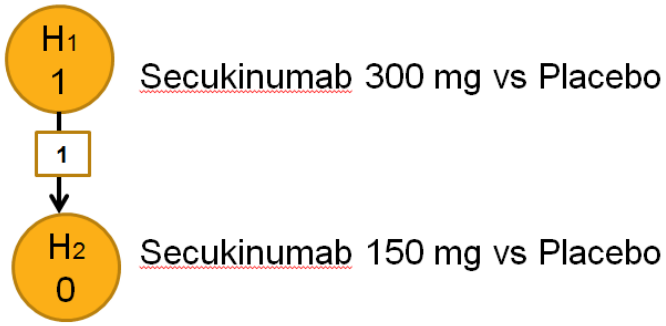
Testing strategy

The family-wise error will be set to α=5% (2-sided). H1 is tested at α (2-sided). The graphical approach of Bretz (Bretz et al 2009) for sequentially rejective testing procedures is used to illustrate the hierarchical testing strategy (Figure 9-1).

The following hypothesis will be tested sequentially and are included in the hierarchical testing strategy and type-I-error will be set such that a family-wise type-I-error of 5% is kept:

The testing sequence will continue to H2 at α (2-sided) only if H1 has been rejected.

Figure 9-1 Testing strategy



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

9.4.3 Handling of missing values/censoring/discontinuations

Missing data for ASAS20 response and other binary efficacy variables (e.g. ASAS40, ACR 20, BASDAI 50, HAQ-DI©, etc.) for data up to Week 12 will be handled by multiple imputations. Multiple imputation is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. Within this analysis the ACR composites will be imputed and response variables will be derived based on the imputed scores. In the multiple imputation analysis the response status will be imputed based on the individual treatment arm information.

Continuous variables (e.g. ACR components, [redacted].) will be analyzed using a mixed-effects repeated measures model (MMRM) which is valid under the missing at random assumption. For analyses of these parameters, if all post-Baseline values are missing then these missing values will not be imputed and this patient will be removed from

[redacted]

the analysis of the corresponding variable, i.e. it might be that the number of patients providing data to an analysis is smaller than the number of patients in the FAS.

9.4.4 Sensitivity analyses

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

In order to determine the robustness of the logistic regression model used for the primary analysis, ASAS20 response at Week 12 may also be evaluated using a non-parametric analysis of covariance (ANCOVA) model (Koch et al 1998) 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 on response.

The impact of missing data on the analysis results may be assessed as well by repeating the logistic regression model using ways to handle missing data. These may include, but are not limited to:

a. Missing assessment as a responder if patient has met the response criteria already at the time of drop-out, otherwise non-responder.
b. Observed data analysis

The details will be provided in the statistical analysis plan.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The secondary efficacy variables are described below. All secondary efficacy variables will be analyzed using the FAS population.

9.5.1.1 ASAS 40 at Week 12

Response to ASAS 40 at Week 12 will be evaluated using a logistic regression model with treatment and concomitant MTX intake status as factors.

9.5.1.2 BASDAI 50 at Week 12

BASDAI 50 response is defined as at least a 50% improvement (decrease) in total BASDAI score, as compared to the Baseline total BASDAI score (Braun et al 2003; Rudwaleit et al 2004).

Response to BASDAI 50 will be evaluated at Week 12 by the logistic model analogous to the primary endpoint.

9.5.1.3 Spinal pain (VAS) at Week 12

The patient's assessment of back pain will be performed using a 100 mm VAS ranging from no pain to unbearable pain.

[redacted]

Spinal pain assessment will be evaluated over Week 12 by using an ANCOVA model with treatment group, visit and concomitant MTX intake status, as factors and baseline VAS as continuous covariate.

9.5.1.4 SPARCC enthesitis index at Week 12

The SPARCC (Maksymowych et al 2009) enthesitis index focuses on the clinical evaluation and validation of the 16 sites shown in Table 6-3.

SPARCC enthesitis index will be evaluated over Week 12 by using an ANCOVA model with treatment group, visit and concomitant MTX intake status, as factors and baseline SPARCC index as continuous covariate.

9.5.1.5 Physical function index (HAQ-DI©) at Week 12

See Section 9.5.4.1 for details.

9.5.1.6 FACIT-Fatigue© at Week 12

See Section 9.5.4.2 for details.

9.5.1.7 ASAS Health Index at Week 12

See Section 9.5.4.3 for details.

9.5.1.8 ACR 20 response at Week 12

The ACR response (Appendix 9) will be used to determine efficacy (Felson et al 1995).

Response to ACR 20 at Week 12 will be evaluated using a logistic regression model with treatment and concomitant MTX intake status as factors.

9.5.2 Testing strategy for secondary variables

The following hypotheses will be tested for secondary variables

- H_{3a}: secukinumab 300 mg treatment group is not different to placebo group with respect to ASAS40 response at Week 12
- H_{3b}: secukinumab 150 mg treatment group is not different to placebo group with respect to ASAS40 response at Week 12
- H_{4a}: secukinumab 300 mg treatment group is not different to placebo group with respect to BASDAI 50 response at Week 12
- H_{4b}: secukinumab 150 mg treatment group is not different to placebo group with respect to BASDAI 50 response at Week 12
- H_{5a}: secukinumab 300 mg treatment group is not different to placebo group with respect to spinal pain (VAS) response at Week 12
- H_{5b}: secukinumab 150 mg treatment group is not different to placebo group with respect to spinal pain (VAS) response at Week 12
- H_{6a}: secukinumab 300 mg treatment group is not different to placebo group with respect to SPARCC enthesitis index at Week 12

[redacted]

- H_{6b}: secukinumab 150 mg treatment group is not different to placebo group with respect to SPARCC enthesitis index at Week 12
- H_{7a}: secukinumab 300 mg treatment group is not different to placebo group with respect to HAQ-DI© at Week 12
- H_{7b}: secukinumab 150 mg treatment group is not different to placebo group with respect to HAQ-DI© at Week 12
- H_{8a}: secukinumab 300 mg treatment group is not different to placebo group with respect to FACIT-Fatigue© score at Week 12
- H_{8b}: secukinumab 150 mg treatment group is not different to placebo group with respect to FACIT-Fatigue© score at Week 12
- H_{9a}: secukinumab 300 mg treatment group is not different to placebo group with respect to ASAS Health index at Week 12
- H_{9b}: secukinumab 150 mg treatment group is not different to placebo group with respect to ASAS Health index at Week 12
- H_{10a}: secukinumab 300 mg treatment group is not different to placebo group with respect to ACR 20 response at Week 12
- H_{10b}: secukinumab 150 mg treatment group is not different to placebo group with respect to ACR 20 response at Week 12

9.5.3 Safety variables

9.5.3.1 Adverse events

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

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

AE summaries may be presented separately by study periods.

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

Separate summaries will be provided for death, SAE, other significant AEs leading to discontinuation and AEs leading to dose adjustment (including study treatment discontinuation).

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

[redacted]

For AEs of special interest time-to-event analysis will be performed, as appropriate and as described in the statistical analysis plan. Results will be tabulated and the Kaplan-Meier estimates for the cumulative rate will be plotted.

9.5.3.2 Laboratory data

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

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

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

9.5.3.3 Vital signs

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

9.5.4 Health-related quality of life

Variables related to health-related quality of life (HR-QoL) are described below. All HR-QoL variables will be evaluated based on FAS.

9.5.4.1 Health assessment questionnaire – disability index at Week 12

The disability index (HAQ-DI©) will be evaluated over Week 12 using an ANCOVA model with treatment group, visit and concomitant MTX intake status, as factors and baseline HAQ-DI© index as continuous covariate.

9.5.4.2 FACIT-Fatigue© score at Week 12

The FACIT-Fatigue© total score will be evaluated over Week 12 using an ANCOVA model analogous to HAQ-DI© analysis.

9.5.4.3 ASAS Health Index at Week 12

The ASAS health index is a linear composite measure and contains 17 items (dichotomous response option: "I agree" and "I do not agree"), which cover most of the ICF core set for AS

[redacted]

(Kiltz et al 2014). It will be evaluated over Week 12 using an ANCOVA model analogous to HAQ-DI© analysis.

[redacted]

[redacted]

9.8 Sample size calculation

The selected criterion for the primary objective, the ASAS 20 score, is intended to be used in patients with axial skeleton involvement. Consequently, secukinumab data available from previous studies on this outcome measure, related to AS patients, can be taken into account. Compared to PsA patients, in AS patients the peripheral joints involvement is less pronounced. Thus the ASAS 20 score for AS patients is expected to capture information entirely related to the axial skeleton involvement. Patients with PsA who will be included in the present study, are characterized by concomitantly experiencing axial and peripheral joints disease. Thus the ASAS 20 score is expected to also reflect the peripheral joints components.

To assume the magnitude of ASAS 20 response for PsA patients treated with secukinumab data from CAIN457F2310 (AS patients) and the CAIN457F2312 (PsA patients) have been considered.

The CAIN457F2310 study compared secukinumab to placebo in AS patients, and the ASAS 20 response rate at Week 12 was 57% for 150 mg secukinumab and 28% for placebo (300mg secukinumab was not tested). These results are a basis to extrapolate the expected results for the current study.

In a phase 3 study of Secukinumab in PsA patients, CAIN457F2312, the performance of 300 mg secukinumab is, compared to 150 mg secukinumab, numerically better in the achievement of the ACR 20 score. Assuming comparable trends in treatment response of the spine and the peripheral joints, a slightly different response between the 300 mg and the 150 mg treatment group was chosen. In addition, from data available in the literature (Lubrano and Spadaro 2012) it appears that the spinal involvement in PsA is milder compared to AS in terms of inflammation and impact on physical function, so that it can be expected that PsA patients might more easily achieve an ASAS 20 score compared to AS patients.

Similarly we can assume, that placebo response rates in AxPsA patients may be higher compared to AS.

For the 150 mg secukinumab treatment group a response rate of 57% is expected at Week 12.

For the 300 mg secukinumab treatment group a response rate of 60% is expected at Week 12.

An overall type I error (2-sided) 5% will be used to control type I error. Since two secukinumab doses will be tested versus placebo in a hierarchical manner, no type-I-error adjustment is required for each comparison with respect to the primary endpoint (ASAS20 response at Week 12). To achieve 92% power and assuming conservatively a response rate of 40% in the placebo group, at least 150 patients per group would be needed under equal allocation to show a response rate of 60% in the secukinumab 300 mg group. Using the same number of patients per group, the second test will have at least 80% power to detect a difference, if the true response rates are 57% in secukinumab 150 mg group and 40% in placebo. The above sample size calculation is based on Fisher's exact test.

To compensate for drop-outs and protocol violations, 165 patients per group (=495 total) should be recruited into this trial.

SAS version 9.4 software was used for the calculation of sample size.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

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

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

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

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

10.4 Publication of study protocol and results

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

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance (CQA), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

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

11 Protocol adherence

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

[redacted]

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

11.1 Protocol amendments

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

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[redacted]

13 Appendix 1: Clinically notable laboratory values

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

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

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

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

[redacted]

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

Table 14-1 Liver event and laboratory trigger definitions

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

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Table 14-2 Follow-up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

[redacted]

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

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

[redacted]

15 Appendix 3: Specific renal alert criteria and actions

Table 15-1 Specific renal alert criteria and actions

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

16 Appendix 4: Classification criteria for psoriatic arthritis

To meet the ClASsification of Psoriatic ARthritis (CASPAR) criteria for diagnosis of psoriatic arthritis according to Taylor et al 2006, a subject must have inflammatory articular disease (joint, spine or entheseal) and at least 3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis **(2 points)**.
   - Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.†
   - A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider.
   - A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.
2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination **(1 point)**.
3. A negative test result for the presence of rheumatoid factor by any method except latex **(1 point)**.
4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist **(1 point)**.
5. Radiographic evidence of juxta-articular new bone formation appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot **(1 point)**.

Total score: _____

(The CASPAR criteria eCRF will autopopulate the total number of points of the CASPAR criteria met by the subject. If the total score ≥ 3, the subject meets CASPAR criteria for PsA diagnosis.)

† Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

[redacted]

17 Appendix 5: Assessment of Spondyloarthritis International Society (ASAS) criteria

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

1. Patient's global assessment of disease activity measured on a VAS scale.
2. Patient's assessment of IBP, 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. Morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI regarding morning stiffness as measured by VAS scale.

17.1 Bath ankylosing spondylitis functional index (BASFI)

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

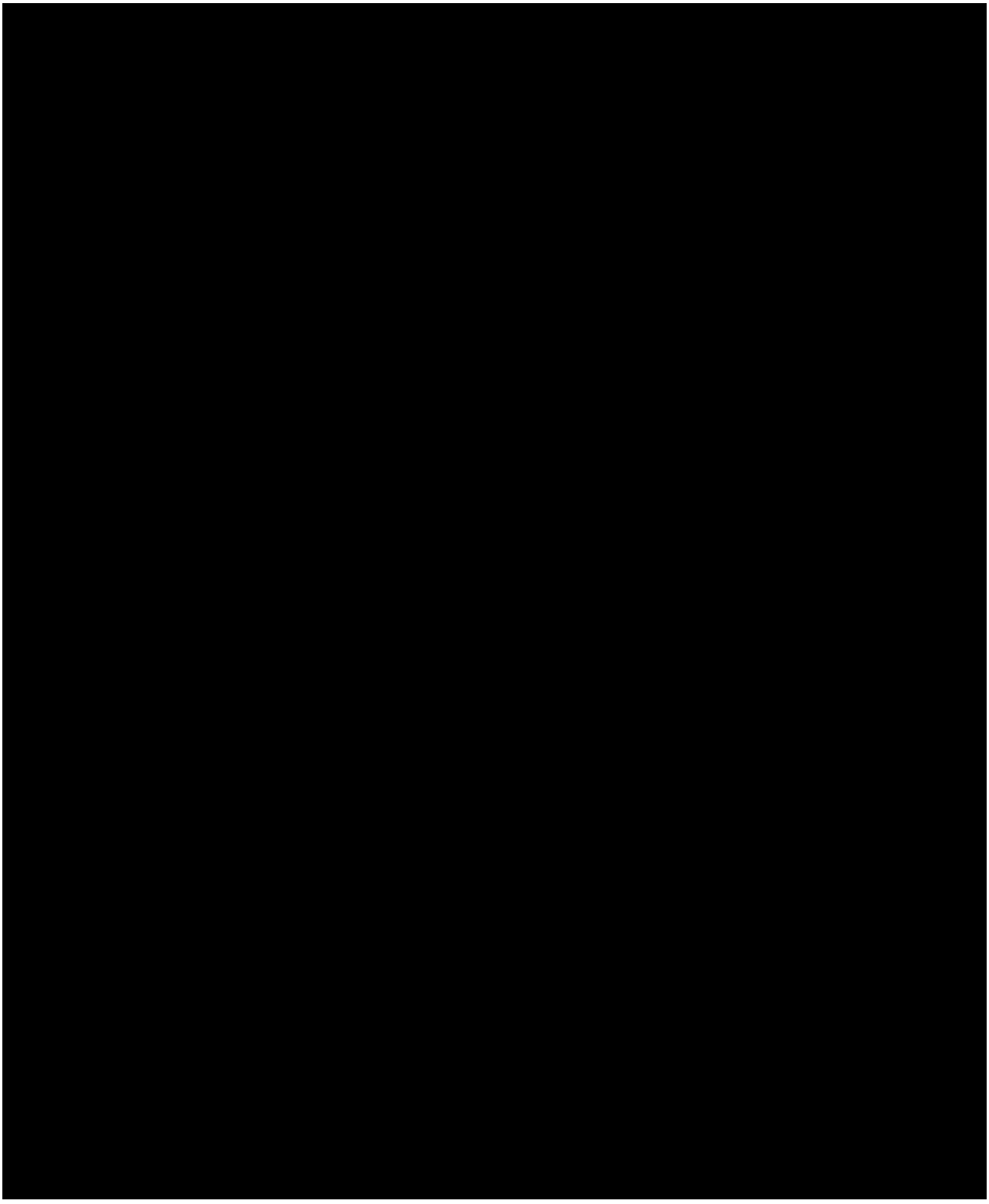
17.2 Bath ankylosing spondylitis disease activity Index (BASDAI)

The gold standard for measuring and evaluating disease activity in AS is the BASDAI. The BASDAI consists of a one through 10 scale (0 being no problem and 10 being the worst problem, captured as a continuous VAS), which is used to answer 6 questions pertaining to the 5 major symptoms of AS:

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

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

[redacted]



19 Appendix 7: Health assessment questionnaire – disability index (HAQ-DI©)

The HAQ© (Fries et al 1980) is a validated measure of physical disability and functional status. It has four dimensions: disability, pain, drug side effects and dollar costs, although, the latter three are rarely used in clinical trials. In this trial only the disability dimension will be used. The disability dimension consists of 20 multiple choice items concerning difficulty in performing eight common activities of daily living; dressing and grooming, arising, eating, walking, reaching, personal hygiene, gripping and activities. Patients choose from four response categories, ranging from 'without any difficulty' to 'unable to do'. The ACR Rheumatology Committee on Outcome Measures in RA recommends the use of this questionnaire in clinical trials.

Scoring of the HAQ©

The HAQ© will be scored in accordance with the recommendation from the developers outlined in the "HAQ PACK" from Stanford University, California.

The following coding (Table 19-1) is to be used for the 8 categories of the disability outcome dimension:

Table 19-1 Coding for disability outcome dimension

Without ANY Difficulty	0
With SOME Difficulty	1
With MUCH Difficulty	2
UNABLE to do	3

Within each of the 8 categories only the item indicating the most severe impairment contributes to the category score. If the patient requires the use of aids, devices, or help from another to accomplish any of the activities in an associated category, then the score for that category will be assigned the value 2, unless the score is already 3 (i.e. scores of 0 or 1 are increased to 2). Associated categories are defined in the "HAQ PACK". From the scores for each category a Standard Disability Index (SDI) is computed by summing the computed scores for each category and dividing by the number of categories answered. The SDI is not computed if the patient does not have scores for at least 6 categories. This SDI is the HAQ© score, which will be used in the statistical analyses of this instrument. The range for this score is (0, 3).

HAQ© Data Collection

The HAQ© is to be completed by the patients in their local languages, using an electronic device. The questionnaires should be completed by the patients in a quiet area free from disturbance, and before any visit assessments. Patients should receive no help from family members; if questions cannot be answered alone (due to problems with reading or understanding), then the doctor or nurse should read the questions and record the patient's

[redacted]

responses without influencing their answers. The information provided is strictly confidential and will be treated as such. If a patient has missed a question or given more than one response per question, then this should be brought to patient. Incomplete questions should not be accepted without first encouraging the patient to complete unanswered questions.

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

[redacted]

20 Appendix 8: ASAS recommendations for collecting, analyzing and reporting NSAID intake

Table 20-1 ASAS-NSAID equivalent score

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

Source: Dougados et al 2011

Results of the survey evaluating the opinion of ASAS members about the comparable efficacy of each NSAID with 150 mg of diclofenac.

Values given are:

*first row, n-number of ASAS members giving an answer to the question;

second row, median dose in mg (tertiles)

† first row, n=number of ASAS members who have voted in favour of such a dose/the total number of ASAS members who have voted; second row, agreed dose.

AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; NSAID, non-steroidal anti-inflammatory drug

[redacted]

21 Appendix 9: American College of Rheumatology measures and criteria of response

Number of tender joints

Joint counts will be performed by the independent assessor(s) who must be well trained and part of the site personnel. Whenever possible, the same evaluator should perform these assessments at all visits.

The 78 joints assessed for tenderness include the 2 temporomandibular, 2 sternoclavicular, 2 acromioclavicular joints, 2 shoulders, 2 elbows, 2 wrists, 2 first carpometacarpal, 10 metacarpophalangeal, 10 proximal interphalangeal, 8 distal interphalangeal joints of the hands, the 2 hip, 2 knee, 2 talo-tibial, 2 mid-tarsal, 10 metatarsophalangeal, 10 proximal interphalangeal, and 8 distal interphalangeal joints of the feet.

Joint tenderness and swelling are to be graded present (1) or absent (0).

Number of swollen joints

Joints are to be scored as either swollen (1) or not swollen (0). The 76 joints to be examined for swelling are the same as those examined for tenderness, however excluding both hip joints.

Patient's assessment of psoriatic arthritis pain

On a 100 mm non-anchored VAS, from no pain to unbearable pain.

Patient's global assessment of disease activity

On a 100 mm non-anchored VAS, from no arthritis activity to maximal arthritis activity, after the question "Considering all the ways your arthritis affects you, draw a line on the scale for how well you are doing."

Physician's global assessment of disease activity

On a 100 mm non-anchored VAS, from no arthritis activity to maximal arthritis activity.

Patient's assessment of physical function

Health Assessment Questionnaire – HAQ-DI©.

ACR 20/50/70*

A patient will be considered as improved according the ACR 20 criteria* if she/he has at least 20% improvement in the 2 following measures:

- Tender joint count (TJC)
- Swollen joint count (SJC)
- and at least 3 of the following 5 measures:
  - Patient's assessment of pain
  - Patient's global assessment of disease activity
  - Physician's global assessment of disease activity

[redacted]

- Health assessment questionnaire (HAQ©) score
- [redacted] erythrocyte sedimentation rate [redacted]

ACR 50 = 50% improvement in at least 3 of the 5 measures and 50% improvement in the swollen and tender joint count.

ACR 70 = 70% improvement in at least 3 of the 5 measures and 70% improvement in the swollen and tender joint count.

Source: Felson et al 1995.

[redacted]