NOVARTIS

Global Clinical Development - General Medicine

AIN457/Secukinumab

Clinical Trial Protocol CAIN457F3301 / NCT02771210

A randomized, double-blind, placebo-controlled multicenter study of subcutaneous secukinumab to demonstrate efficacy in the treatment of enthesitis at the Achilles tendon up to 1 year in adult patients with active Psoriatic Arthritis (PsA) and axial Spondyloarthritis (axSpA) (ACHILLES)

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ALT/SGPT	Alanine aminotransferase/serum glutamic pyruvic transaminase
ANCOVA	Analysis of covariance
Anti-CCP	Anti-cyclic citrullinated peptide
AS	Ankylosing Spondylitis
ASAS	Assessment of Spondyloarthritis International Society
[redacted]	[redacted]
axSpA	axial Spondyloarthritis
AST/SGOT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase
BASDAI	Bath ankylosing spondylitis disease activity index
[redacted]	[redacted]
CASPAR	Classification criteria for Psoriatic Arthritis
CRO	Contract Research Organization
CRP	C-reactive protein
DMARD	Disease Modifying Anti-rheumatic Drug
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
eCRF	electronic Case Report/Record Form
EMA/EMEA	European Medicines (Evaluation) Agency
[redacted]	[redacted]
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
[redacted]	[redacted]
hCG	human chorionic gonadotropin
HIV	Human immunodeficiency virus
HLA-B27	Human Leukocyte Antigen B27
HRQoL	Health-related Quality of Life
hsCRP	High sensitivity C-Reactive Protein
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions for Use
IL	Interleukin
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
i.v.	intravenous(ly)
LEI	Leeds Enthesitis Index
LFT	Liver function test (raised serum transaminases and/or bilirubin levels)

[redacted]

MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
[redacted]	[redacted]
MRI	Magnetic resonance imaging
MTX	Methotrexate
NRS	Numerical rating scale
NSAID	Non-steroidal anti-inflammatory drug
PCS	Physical Component Summary
PFS	Prefilled syringe
PRN	pro re nata
PRO	Patient Reported Outcome
PsA	Psoriatic arthritis
PsAMRIS	Psoriatic Arthritis Magnetic Resonance Imaging Score
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAE	Serious adverse event
s.c.	Subcutaneous(ly)
SF-36	Medical Outcome Short Form (36) Health Survey
SJC	Swollen Joint Count
SmPC	Summary of Product Characteristics
SpA	Spondyloarthritis
SUSAR	Suspected Unexpected Serious Adverse Reactions
TJC	Tender Joint Count
TNF/TNFα	Tumor necrosis factor
TNF IR / TNFα-IR	TNFα inhibitor inadequate responder
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cell

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial.
DMARD	Disease modifying anti-rheumatic drug; in this study this term refers only to non-biologics.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Inadequate response to TNFα	Active disease despite stable treatment with anti-tumor necrosis factor α (TNFα) for at least 3 months at a stable dose or for at least one dose in the case of lack of tolerance.
Study drug	The drug whose properties are being tested in the study; this definition is consistent with US Code of Federal Regulation 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Study treatment	All study drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Study treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication.
Medication number	A unique identifier on the label of each 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.
Period	The planned stage of the patient’s participation in the study. Each period serves a purpose in the study as a whole.
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.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment.
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.
Responder	A patient with ≥ 20% improvement from Baseline in both tender joint count (TJC) and swollen joint counts (SJC).

[redacted]

Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal.
Patient number	A number assigned to each patient who enrolls into the study.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study.

[redacted]

Amendment 3

Amendment rationale

The main purpose of this amendment is to allow inclusion of patients, who have been exposed to TNFα inhibitors before the study. This change is warranted based on feedback from the investigators. This amendment aims to better reflect the entire population of PsA and axSpA patients with achilles tendon enthesitis in the study.

The change in the study eligibility criteria does not affect the sample size calculation as this was based on the data from study CAIN457F2312 which also allowed the inclusion of up to 40% TNF-IR patients. Therefore, the sample size in CAIN457F3301 does not change.

Eligibility criteria incl. definitions of wash out periods were added accordingly. [redacted] The duration of screening phase was extended to up to 10 weeks in order to align with duration of wash out period of specific TNFα inhibitors. Subsequently the section describing the prohibited medication was also updated.

Further adaptations of eligibility criteria were made for clarification purposes and to remove inconsistencies.

The requirement of dedicated renal safety monitoring was removed as up to now there has been no safety signal for nephrotoxicity with secukinumab in over 12,000 patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the kidney. This is also aligned with previous secukinumab phase III studies in PsA and AS. Consequently the related appendix 3 (Specific Renal Alert Criteria and Actions) was deleted.

The assessment scheduled was updated in a new format and some inconsistencies were resolved.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions. The wording of various sub-sections to "Introduction" (Section 1), "Study objectives and endpoints" (Section 2), "Investigational Plan" (Section 3), "Population" (Section 4), "Treatment" (Section 5), "Visit schedule and assessments" (Section 6), "Safety Monitoring" (Section 7), "Data review and database management" (Section 8), and "Data analysis" (Section 9) have been amended to reflect the rationale given above.

A selection of the main changes encompasses:

- [redacted]
- Section 3.1 - Study design: information was added that it is planned to enroll no more than 40% TNF-IR patients in the study. Also figure 3-1 (study design) was updated to reflect the screening period of 10 weeks.

[redacted]

- Section 4.1 - Inclusion criteria:
  - Inclusion criterion #3 has been changed to change the number of tender as well as of swollen joints in patients with active PsA to ≥ 1
  - Inclusion criterion #6 has been updated in order to remove the limit of up to 5 years at Baseline regarding the duration of onset of heel pain
  - Inclusion criterion #8: has been updated in order to include TNF-inhibitors in the definition of standard treatments.
  - Inclusion criterion #10: the duration of use of NSAIDs has been rephrased and TNF-inhibitors have been included to describe required pre-treatment.
  - Inclusion criterion #16 was added to clarify, that patients must have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months prior to randomization or have been intolerant to at least one administration of an anti-TNFα agent
  - Inclusion criterion #17 was added to define the wash-out periods appropriate for the different TNF-inhibitors.
- Section 4.2 – Exclusion criteria:
  - Exclusion criterion #9 has been updated to describe, that Patients who have previously been treated with more than two (2) TNF inhibitors (investigational or approved) are not eligible for the study.
  - Exclusion criterion #10 has been updated to clarify, that pre-treatment with biologic immunomodulating agents, except those targeting TNFα, is not allowed.
  - Exclusion criterion #10 has been changed in order to clarify an inconsistency. The contraception methods, that are acceptable in this study, are defined as effective contraception methods.
- Section 5.2 – Treatment arms: updates were included to describe the secukinumab/placebo dose for patients previously exposed to TNF inhibitors.
- Section 5.3 - Treatment assignment and randomization: the information was added, that it is planned to enroll no more than 40% TNF-IR patients in the study.
- Section 5.5.8 – Prohibited medication: Table 5-1 has been updated to include information on TNF-inhibitors. It was also clarified, that use of analgesics (NSAIDs, low strength opioids, paracetamol/acetaminophen) PRN is not allowed until week 24.
- Section 6 - Visit schedule and assessments:
  - Table 6-1 Assessment schedule: the table was updated in a new format and some inconsistencies were corrected.
- Section 7.4 – Renal safety monitoring: this paragraph has been updated as described above
- Appendix 3 - Specific Renal Alert Criteria and Actions has been deleted due to rationale described above. All subsequent appendices have been newly numbered.
- Appendix 3 (new numbering) - The classification criteria for psoriatic arthritis (CASPAR): some information has been added to increase clarity how this score is to be calculated.

[redacted]

Additionally, this protocol amendment includes 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 changes herein affect the Informed Consent. Therefore, a revised Informed Consent that takes into account the changes described in this protocol amendment will be provided and submitted for approval. None of the changes described in this amended protocol are made due to newly emerged safety considerations.

[redacted]

Amendment 2

Amendment rationale

This protocol amendment is issued to remove an inconsistency within exclusion criterion #13 and to clarify that vital signs should be measured at every visit at which hematology and blood chemistry samples are taken

- To correct the inconsistency of exclusion criterion #13: The contraceptive methods, women of child-bearing potential are required to use, are effective methods of contraception (according to Clinical Trial Facilitation Group (CTFG) guidance). The term "highly effective methods" has therefore been corrected to "effective methods". The listing of acceptable methods described in exclusion criterion #13 already reflected the requirement for "effective methods of contraception" and are aligned with previous Phase III trials of secukinumab.
- To clarify that vital sign assessments should be performed at all visits at which hematology and blood chemistry samples are taken.

Changes to the protocol

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

- Section 4.2: clarification of exclusion #13: The term "highly effective methods" has been corrected to "effective methods"
- Section 6, Table 6-1: Addition of vital signs at visit 4 (week 2), visit 6 (week 4), visit 8 (week 12), and visit 10 (week 20), documented in source documentation.

Additionally, this protocol amendment includes 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 changes herein affect the Informed Consent. Therefore, a revised Informed Consent that takes into account the changes described in this protocol amendment will be provided and submitted for approval. None of the changes made are due to safety concerns and none of the changes have an impact on the conduct of the trial or alter in any way the treatment of study subjects.

At the time this amendment was written the study was approved in Germany by health authority (Paul-Ehrlich-Institut) as well as ethics committee.

[redacted]

Amendment 1

Amendment rationale

This protocol amendment is issued for the following reasons:

- To add central laboratory testing, including hematology and blood chemistry, as well as urine testing at the screening visit in the assessment schedule (Table 6-1 Assessment schedule). These tests were outlined in exclusion criteria 17-19 already before and results of these tests determine eligibility for the study. Thus, the addition to the assessment schedule in this amendment is made in order to clarify and remove inconsistencies in the trial protocol.
- To clarify that approximately 50% of randomized patients should be PsA and axSpA patients respectively in order to allow randomization of all eligible patients in screening at time point of enrollment stop.
- To clarify that patients who are unable or unwilling to undergo MRI examination of the affected foot are not eligible for the study. This was already outlined in section (6.4.1.7 Magnetic resonance imaging) before. As all patients will be subject to MRI imaging in this study, this is now also reflected in the inclusion and exclusion criteria.
- To clarify that there will be no Gadolinium contrast agent used for MRI scans performed in this study.

Changes to the protocol

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

- Section 4.2: Addition of exclusion #30: Clarification that patients unable or unwilling to undergo MRI scans are not eligible for this study.
- Section 5.5: Modified wording to reflect that it is targeted that approximately 50% of randomized patients should be PsA and axSpA patients respectively.
- Section 6, Table 6-1: Addition of assessment hematology, blood chemistry, urinalysis at screening visit.
- 6.4.1.7 Magnetic resonance imaging: Deletion of gadolinium containing contrast agent.

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 changes herein affect the Informed Consent. Therefore, a revised Informed Consent that takes into account the changes described in this protocol amendment will be provided and submitted for approval. None of the changes made are due to safety concerns and none of the changes have an impact on the conduct of the trial or alter in any way the treatment of study subjects.

At the time this amendment was written no patient has been enrolled in the study.

[redacted]

Protocol summary

Protocol number	CAIN457F3301
Title	A randomized, double-blind, placebo-controlled multicenter study of subcutaneous secukinumab to demonstrate efficacy in the treatment of enthesitis at the Achilles tendon up to 1 year in adult patients with active Psoriatic Arthritis (PsA) and axial Spondyloarthritis (axSpA) (ACHILLES)
Brief title	Study of efficacy and safety of secukinumab in PsA and axSpA patients with active enthesitis including one Achilles tendon site
Sponsor and Clinical Phase	Novartis and Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to demonstrate efficacy, including effects on inflammation by magnetic resonance imaging (MRI) assessments, of secukinumab on Achilles tendon enthesitis for up to 1 year with a primary focus at Week 24, in patients with active PsA and axSpA despite current or previous non-steroidal anti-inflammatory drugs (NSAID) and/or disease modifying anti-rheumatic drug (DMARD) and/or anti-TNFα therapy. Data from this study are aimed at broadening secukinumab's profile as a novel treatment option for PsA and axSpA patients with active enthesitis including one Achilles tendon site.
Primary Objective	To demonstrate that the efficacy of secukinumab is superior to placebo based on the percentage of patients with resolution of Achilles tendon enthesitis as assessed by the respective subcomponent of the Leeds enthesitis index (LEI) at Week 24 in patients with active PsA and axSpA.
Secondary Objectives	Secondary objectives are to evaluate: 1. The efficacy of secukinumab at Week 24 is superior to placebo based on the mean change of heel pain measured on a 10-point numerical rating scale (NRS). 2. The efficacy of secukinumab at Week 24 is superior to placebo based on the percentage of patients with an improvement of bone marrow edema in the insertion of the Achilles tendon in the upper part of the calcaneus and/or in the insertion of the plantar aponeurosis in the lower part of the calcaneus as assessed by the respective subcomponent of the Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) in the affected foot at Baseline. 3. The efficacy of secukinumab at Week 24 is superior to placebo based on the percentage of patients with resolution of enthesitis as assessed by the LEI. 4. The efficacy of secukinumab at Week 24 is superior to placebo based on the mean change in physician's global assessment of disease activity. 5. The efficacy of secukinumab at Week 24 is superior to placebo based on the mean change in patient's global assessment of disease activity. 6. The efficacy of secukinumab at Week 24 is superior to placebo based on the mean change in physician's global assessment of heel enthesiopathy activity. 7. The efficacy of secukinumab at Week 24 is superior to placebo based on the mean change in patient's global assessment of heel enthesiopathy activity.

	8. The improvement in secukinumab at Week 24 is superior to placebo based on the change from Baseline in Short Form-36 Physical Component Summary (SF-36 PCS) or SF-36v2. 9. To describe the increase in percentage of patients with resolution of Achilles tendon enthesitis after switching from placebo to secukinumab at Week 24. 10. To describe the increase in mean change of heel pain in patients after switching from placebo to secukinumab at Week 24. 11. The overall safety and tolerability of secukinumab.

[redacted]

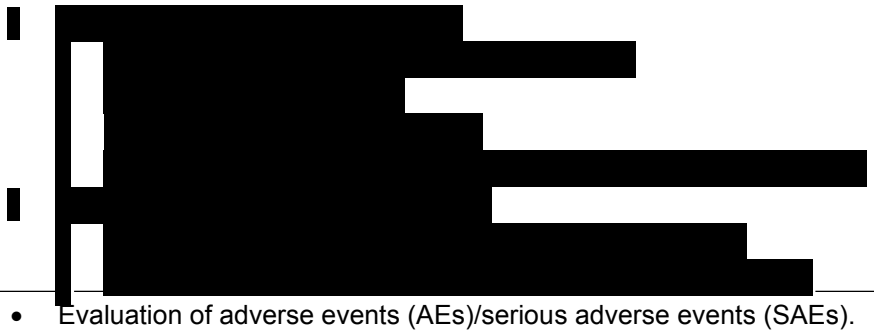
[redacted]

Study design	This is a 52-week, randomized, parallel-group, double-blind, multicenter, international study consisting of a 10-week screening period, a 24-week, placebo-controlled, double-blind treatment period and a 28-week open-label treatment period.
Population	The study population will consist of male and female patients (≥ 18 years old at the time of consent) with active PsA or axSpA presenting active enthesitis including one Achilles tendon site that is refractory to standard treatment. The Achilles tendon enthesitis must be clinically diagnosed and must be MRI-positive according to the investigator`s judgement.

Key Inclusion criteria	Patients eligible for inclusion in this study have to fulfill all of the following key inclusion criteria (please refer Section 4.1 for complete list):
	• Male or non-pregnant, non-lactating female patients at least 18 years of age.
	• PsA patients must fulfill the following criteria:
	  ○ Diagnosis of PsA classified by CASPAR criteria with symptoms for at least 6 months **and**
	  ○ Active PsA as assessed by ≥ 1 tender joints out of 78 and ≥ 1 swollen joints out of 76 at Baseline (dactylitis of a digit counts as one joint each).
	• AxSpA patients must fulfill the following criteria:
	  ○ AxSpA as per the classification of the ASAS axSpA criteria with objective signs of inflammation at Screening, evident by either MRI with Sacroiliac joint inflammation or definite radiographic sacroilitis according to the modified NY criteria (both according to source documentation) and/or hsCRP > ULN (as defined by central lab) **and**
	  ○ Active disease assessed by total BASDAI ≥ 4 (0–10) at Baseline.
	• Diagnosis of Achilles tendon enthesitis according to swelling and tenderness at the insertional site of the Achilles tendon into the calcaneus.
	• Onset of heel pain ≥ 1 month at Baseline.
	• Heel enthesitis that is MRI-positive according to the investigator`s judgement.
	• Patients who have been exposed to up to two TNFα inhibitors.
	• Patients who have previously been on a TNFα inhibitor will be allowed enter into study after an appropriate wash-out period prior to randomization.

Key Exclusion criteria	Patients fulfilling any of the following key exclusion criteria are not eligible for inclusion in this study (please refer Section 4.2 for complete list). 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. Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor. 3. Ongoing use of psoriasis treatments / medications (e.g. topical corticosteroids, UV therapy) at randomization. The following washout periods need to be observed: ○ Oral or topical retinoids: 4 weeks.

[redacted]

	○ Photochemotherapy (e.g. PUVA): 4 weeks. ○ Phototherapy (UVA or UVB): 2 weeks. ○ Topical skin treatments (except in face, eyes, scalp and genital area during Screening, only corticosteroids with mild to moderate potency): 2 weeks. 4. Patients who have previously been treated with more than two (2) TNF inhibitors (investigational or approved). 5. Patients who have ever received biologic immunomodulating agents (investigational or approved), except those targeting TNFα. 6. 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. 7. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by a positive QuantiFERON TB-Gold test. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated.
Study treatment	Study treatment: • Secukinumab 150 mg provided in 1 mL pre-filled syringe (PFS) Placebo: • Secukinumab placebo provided in a 1 mL PFS
Efficacy assessments	• Assessments in all patients: ○ Resolution of Achilles tendon enthesitis as assessed by the respective subcomponent of the Leeds enthesitis index (LEI). ○ Enthesitis assessment (LEI). ○ Heel pain (NRS). ○ Physician`s global assessment of disease activity (VAS). ○ Patient's global assessment of disease activity (VAS). ○ Physician`s global assessment of heel enthesiopathy activity (VAS). ○ Patient's global assessment of heel enthesiopathy activity (VAS). ○ Magnetic Resonance Imaging (MRI) including subcomponents of the Psoriatic arthritis magnetic resonance imaging scoring system (PsAMRIS). 
Key safety assessments	• Evaluation of adverse events (AEs)/serious adverse events (SAEs). • Physical examination. • Vital signs. • Height and weight.

	• QuantiFERON TB-Gold test. • Laboratory evaluations (Hematology, Clinical Chemistry, Urinalysis). • Electrocardiogram (ECG). • Pregnancy and assessment of fertility. • Tolerability of secukinumab.
Other assessments	• Medical outcome short form (36) health survey (SF-36 v2). [redacted] • Human leukocyte antigen B27 (HLA-B27)
Data analysis	The primary endpoint, the resolution of Achilles tendon enthesitis at 24 weeks will be analyzed using a logistic regression model with the factors treatment, TNFα inhibitor status and stratification factor diagnosis (PsA or axSpA).
Key words	Active psoriatic arthritis, axial spondyloarthritides, subcutaneous, secukinumab in prefilled syringe, enthesitis, achilles tendon

[redacted]

1 Introduction

1.1 Background

Psoriatic Arthritis (PsA) and axial Spondyloarthritis (axSpA) are chronic inflammatory diseases which belong to the spectrum of conditions commonly referred to as spondyloarthritides (SpA). While the various SpA may be diverse in their clinical presentations, common environmental as well as genetic factors associated with susceptibility to SpA are suspected (Turkiewicz and Moreland 2007). Axial Spondyloarthritis (axSpA), a form of spondyloarthritis, composed of both non-radiographic axial SpA and AS, and where radiographic sacroiliitis may or may not be present, is among the most common chronic inflammatory joint disorders, with recent estimates of prevalence in Caucasian populations in the range of 1–2% (Baraliakos and Braun 2011). Patients with chronic back pain (onset before 45 years of age) are classified according to the Assessment of Spondyloarthritis international Society (ASAS) classification criteria (Rudwaleit et al 2009) for axSpA if they fulfill either the clinical arm or the imaging arm of the criteria. Psoriatic arthritis is a frequent chronic immune-mediated disease encompassing a spectrum of overlapping clinical entities (Moll and Wright 1973). About 10-40% of patients with psoriasis suffer from PsA. It is not only more common but also more severe than previously thought (Gladman 2004, Taylor et al 2006).

Enthesitis is a frequent manifestation in PsA and SpA and approximately 40% of patients with SpA have enthesitis (Haibel and Sieper 2015). The main clinical manifestations of enthesitis are represented by pain and swelling at the entheseal sites. The pain, in particular, may be severe, persistent and resistent to treatment (D'Agostino et al 2002). Enthesitis is represented by inflammation at the enthesis, which is an anatomical area where ligaments, tendons and joint capsules attach to the bone (D'Agostino and Olivieri 2006). Enthesitis can occur at any site but most frequently localizes in the heel at the 'premiere enthesis', the Achilles tendon (D'Agostino and Olivieri 2006, Haibel and Sieper 2015, D'Agostino et al 2002). In terms of diagnosing enthesitis differential diagnosis should be considered, e.g. mechanical-degenerative causes and fibromyalgia (Haibel and Sieper 2015). Therefore a straightforward approach combining physician-based assessment of Achilles tendon enthesitis with patient-reported outcomes and imaging techniques such as magnetic resonance imaging (MRI) would be the most reliable and appropriate (D'Agostino and Olivieri 2006).

The therapeutic options for enthesitis are limited since only a small number of controlled trials have been performed to date. Non-steroidal anti-inflammatory drugs (NSAID) and local injections of corticosteroids are recommended for treatment of enthesitis although efficacy has only been reported in case studies (Zochling et al 2006, Ritchlin et al 2009). In patients with refractory enthesitis therapeutic approach using NSAIDs, physiotherapy or steroid injections are often not sufficient (D'Agostino et al 2002). For disease modifying anti-rheumatic drugs (DMARD) no efficacy could be demonstrated in small open-label clinical trials (Haibel et al 2005, Haibel et al 2007). Treatment efficacy in PsA/AS associated enthesitis with anti-TNF therapy has been shown using composite indices in clinical trials investigating the overall efficacy, tolerability and safety of anti-TNFα agents in PsA/AS (Kavanaugh et al 2009, Mease et al 2014, van der Heijde et al 2006). A randomized, double-blind, placebo-controlled interventional proof-of-concept trial specifically dedicated to enthesitis has been performed only by one compound so far (Dougados et al 2010). In this

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study efficacy of the TNF antagonist etanercept versus placebo has been studied in 24 SpA patients (as defined by Amor's criteria; Amor et al 1990) that presented heel enthesitis at Baseline including positive MRI according to the local radiologist (Dougados et al 2010). Endpoints of this 12 week trial included patient's global assessment of heel enthesiopathy activity as the primary endpoint as well as heel pain (on a 100-mm visual analogue scale (VAS) scale) and MRI analysis as secondary endpoints. Patient's global assessment of heel enthesiopathy and heel pain showed a statistical significant difference in the etanercept versus placebo group whereas no significant changes were observed in the MRI analysis.

Suboptimal treatment with TNF blockers has been further demonstrated by a retrospective systematic monocenter study that assessed the frequency and effectiveness of switching TNF blockers in SpA and compared patient characteristics with regard to requirement for switching. Interestingly patients who switched the TNF blocker had more peripheral enthesitic symptoms (59.7% switchers versus 40.3% non-switchers, $p = 0.01$) and a tendency for more peripheral involvement (65.3% switchers vs. 51.0% non-switchers, $p = 0.06$) (Dadoun et al 2011). Considered together, these study findings indicate there is still a large unmet medical need for optimal conventional drug treatment in patients suffering from enthesitis and enthesitis-related diseases.

Interleukin (IL) - 17 antagonism represents a novel therapeutic approach aimed at interference with the chronic inflammatory process by selectively targeting the predominant proinflammatory cytokine of the helper T17 cell subset. Over the past years data accumulated that strongly support IL-17 to be a key mediator in enthesial inflammation (Sherlock et al 2012, Lories and McInnes 2012). Several approaches in the pre-clinical setting give a rationale that IL-17 could be the cytokine of interest when specifically targeting enthesitis (Sherlock et al 2012, Ebihara et al 2015, Benham et al 2014). Secukinumab (AIN457) is a high-affinity fully human monoclonal anti-human antibody that neutralizes IL-17A activity that is approved in Europe for the treatment of PsA (involving pivotal Phase III trials: CAIN457F2306 and CAIN457F2312) and AS (involving pivotal Phase III trials CAIN457F2305 and CAIN457F2310).

In the CAIN457F2312 study in patients with PsA, 48.2% and 42.2% of patients treated with secukinumab 300 mg and 150 mg s.c. showed complete resolution of enthesitis at Week 24 versus 21.5% of patients treated with placebo ($P< 0.05$) for those patients with symptoms at Baseline. These responses were sustained and even further increased up to 53.6% (300 mg) and 48.4% (150 mg) at Week 52. Similar findings were obtained in the CAIN457F2306 study in patients with PsA, where 80.0% of patients in the secukinumab 10 mg/kg-75 mg group and 75.0% of patients in the secukinumab 10 mg/kg-150 mg group achieved complete resolution of enthesitis in the enthesitis subset at Week 104. Furthermore in the CAIN457F2305 study in patients with AS, secukinumab showed greater improvement in enthesitis compared with placebo; the change from Baseline in total maastricht ankylosing spondylitis enthesitis score (MASES) was −1.70 for intravenous (IV)-75 mg ($p = 0.0183$) and −1.79 for IV-150 mg ($p = 0.0089$) vs. −0.87 for placebo. The improvements observed at Week 16 in the IV-75 mg and IV-150 mg groups were sustained up to Week 52. However, in the CAIN457F2310 study findings on the MASES index did not consistently show improvements in the secukinumab dose groups compared with placebo. At Week 16, the LS mean change from Baseline in the MASES total score was −0.82 for 150 mg (unadjusted p=0.4264) and −1.43 for 75 mg (unadjusted p=0.5950) vs. −1.19 for placebo. But, the numerical improvements observed at Week 16 in the 75 mg and 150 mg groups were generally sustained up to Week 52.

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Given (1) the suboptimal treatment of refractory enthesitis to date, (2) the crucial role of IL-17 for the inflammatory process at the entheses, and (3) the promising enthesitis data from the large phase III trials of secukinumab great pre-requisites are in place to gain deeper understanding of enthesitis treatment with an anti-IL-17A approach. Therefore this trial would aim for a straightforward approach by (1) focusing on the heel with the Achilles tendon as the primary enthesial site, (2) using physician-based assessment of Achilles tendon enthesitis for the primary endpoint and (3) monitor treatment efficacy by patient-reported outcomes and MRI as a high-resolution imaging technique.

1.2 Purpose

The purpose of this study is to demonstrate efficacy, including effect on inflammation by MRI assessments, of secukinumab on Achilles tendon enthesitis for up to 1 year with a primary focus at Week 24, in patients with active PsA and axSpA despite current or previous NSAID, DMARD and/or anti-TNFα therapy.

Data from this study are aimed at broadening secukinumab's profile as a novel treatment option for PsA and axSpA patients with active enthesitis including one Achilles tendon site.

2 Study objectives and endpoints

2.1 Primary objective

To demonstrate that the efficacy of secukinumab is superior to placebo based on the percentage of patients with resolution of Achilles tendon enthesitis as assessed by the respective subcomponent of the Leeds enthesitis index (LEI) at 24 weeks in patients with active PsA and axSpA.

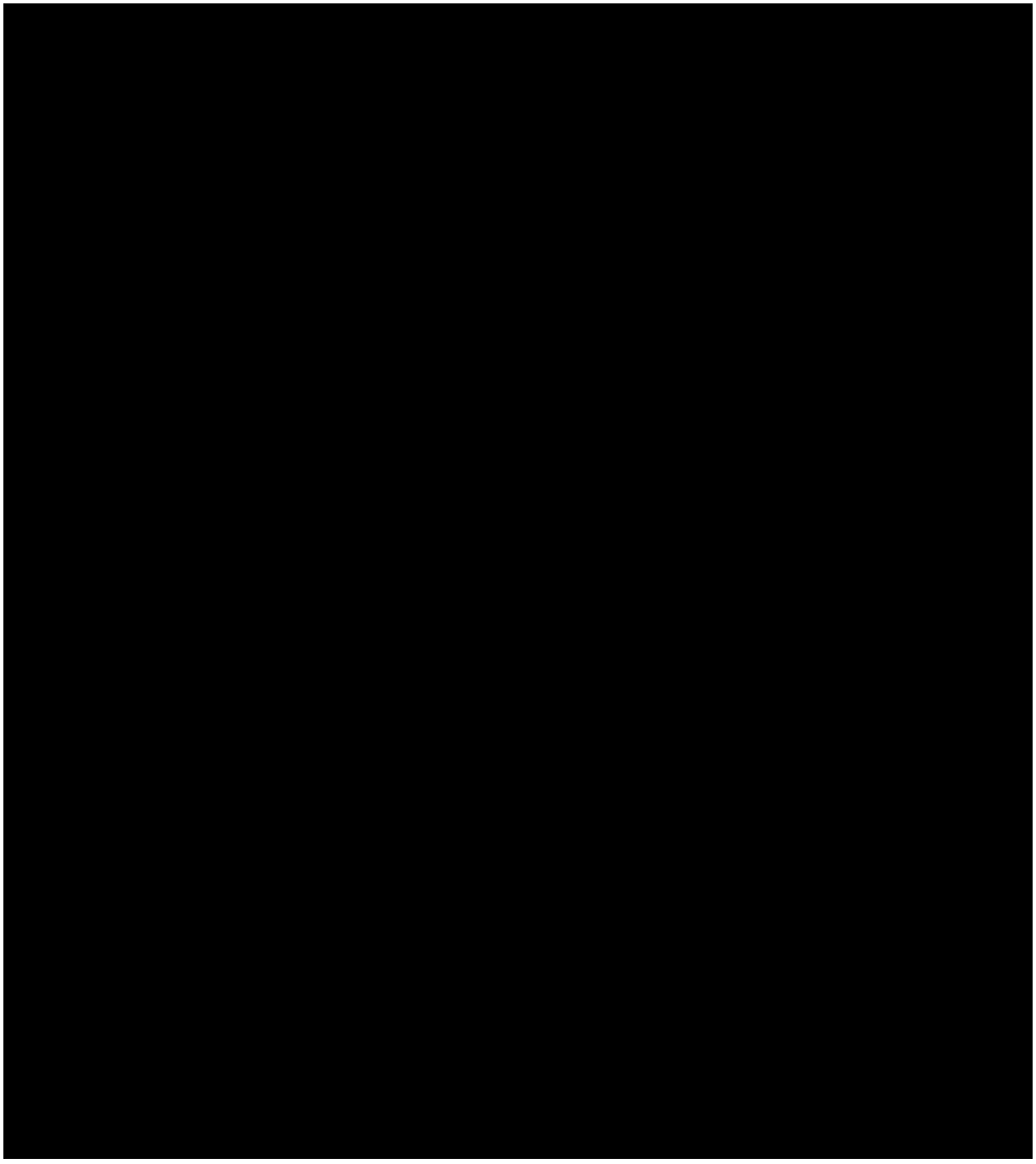
2.2 Secondary objectives

Secondary objectives of the study are to evaluate:

1. The efficacy of secukinumab at Week 24 is superior to placebo based on the mean change of heel pain measured on a 10-point numerical rating scale (NRS).
2. The efficacy of secukinumab at Week 24 is superior to placebo based on the percentage of patients with an improvement of bone marrow oedema in the insertion of the Achilles tendon in the upper part of the calcaneus and/or in the insertion of the plantar aponeurosis in the lower part of the calcaneus as assessed by the respective subcomponent of the Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) in the affected foot at Baseline.
3. The efficacy of secukinumab at Week 24 is superior to placebo based on the percentage of patients with resolution of enthesitis as assessed by the LEI.
4. The efficacy of secukinumab at Week 24 is superior to placebo based on the mean change in physician's global assessment of disease activity.
5. The efficacy of secukinumab at Week 24 is superior to placebo based on the mean change in patient's global assessment of disease activity.
6. The efficacy of secukinumab at Week 24 is superior to placebo based on the mean change in physician's global assessment of heel enthesiopathy activity.

[redacted]

7. The efficacy of secukinumab at Week 24 is superior to placebo based on the mean change in patient's global assessment of heel enthesiopathy activity.
8. The improvement in secukinumab at Week 24 is superior to placebo based on the change from Baseline in Short Form-36 Physical Component Summary (SF-36 PCS) or SF-36v2.
9. To describe the increase in percentage of patients with resolution of Achilles tendon enthesitis after switching from placebo to secukinumab at Week 24.
10. To describe the increase in mean change of heel pain in patients after switching from placebo to secukinumab at Week 24.
11. The overall safety and tolerability of secukinumab.



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3 .Investigational plan

3.1 Study design

This study uses a 2-treatment arm, randomized, parallel-group, double-blind, placebo-controlled design in patients with PsA and axSpA. The dosing of secukinumab will be applied according to the approved European Summary of Product Characteristics (SmPC) in PsA and AS disease. In case of axSpA patients with objective signs of inflammation at screening, evident by either MRI with Sacroiliac joint inflammation (according to source documentation) and/or hsCRP > upper limit of normal (ULN, as defined by central lab) , secukinumab/placebo will be applied as 1 (1.0 mL pre-filled syringe (PFS) of 150 mg dose) s.c. injection. At Baseline approximately 200 patients will be randomized. Randomization will occur to 1 of the following 2 treatment groups in a ratio of 1:1:

- Group 1 (secukinumab): secukinumab as 1 (1.0 mL pre-filled syringe (PFS) of 150 mg dose) s.c. or 2 (2 x 1.0 mL PFS of 150 mg dose, 300 mg) s.c. injections according to axSpA or PsA disease (including extent of psoriasis and TNF-inhibitor status) at Baseline, Weeks 1, 2, and 3, followed by administration every 4 weeks starting at Week 4.
- Group 2 (placebo): placebo as 1 (1.0 mL PFS) or 2 (2 x 1.0 mL PFS) s.c. injections according to axSpA or PsA disease (including extent of psoriasis and TNF-inhibitor status) at Baseline, Weeks 1, 2, 3, followed by administration every 4 weeks starting at Week 4.

Additionally, it is planned to enroll no more than 40% TNF-IR patients in the study.

Starting at Week 24, patients who have been randomized to placebo at Baseline will all switch to secukinumab. They will receive the dose according to their disease (PsA or axSpA). Therefore they will receive secukinumab 150 mg (1.0 mL PFS of 150 mg dose s.c.) or 300 mg (2 x 1.0 mL PFS of 150 mg dose s.c.). Secukinumab will be administered without a loading phase every 4 weeks (Figure 3-1). Thus, starting at Week 24, patients in both groups will receive secukinumab either 150 mg or 300 mg as 1 or 2 injections of 1 mL/150 mg in PFS in an open-label fashion until Week 52 (last dose given at Week 48). However, original randomized treatment assignment to secukinumab or placebo will remain double-blinded to all patients, investigators, and site personnel, whereas the Sponsor (including the Region Europe Clinical Team, statisticians and data management) will be unblinded after the Week 24 database lock (see Section 3.5) and analyses are completed (see Section 9.7).

After the Week 52 database lock and analyses have been completed, investigators, site personnel and patients may be unblinded to the original randomized treatment assignment at Baseline. nr-axSpA patients with objective signs of inflammation at Screening, evident by either MRI with sacroiliac joint inflammation (according to source documentation) and/or hsCRP > ULN (as defined by central lab) who successfully complete the 1 year trial duration and were benefiting from secukinumab may be given the opportunity to enter an extension

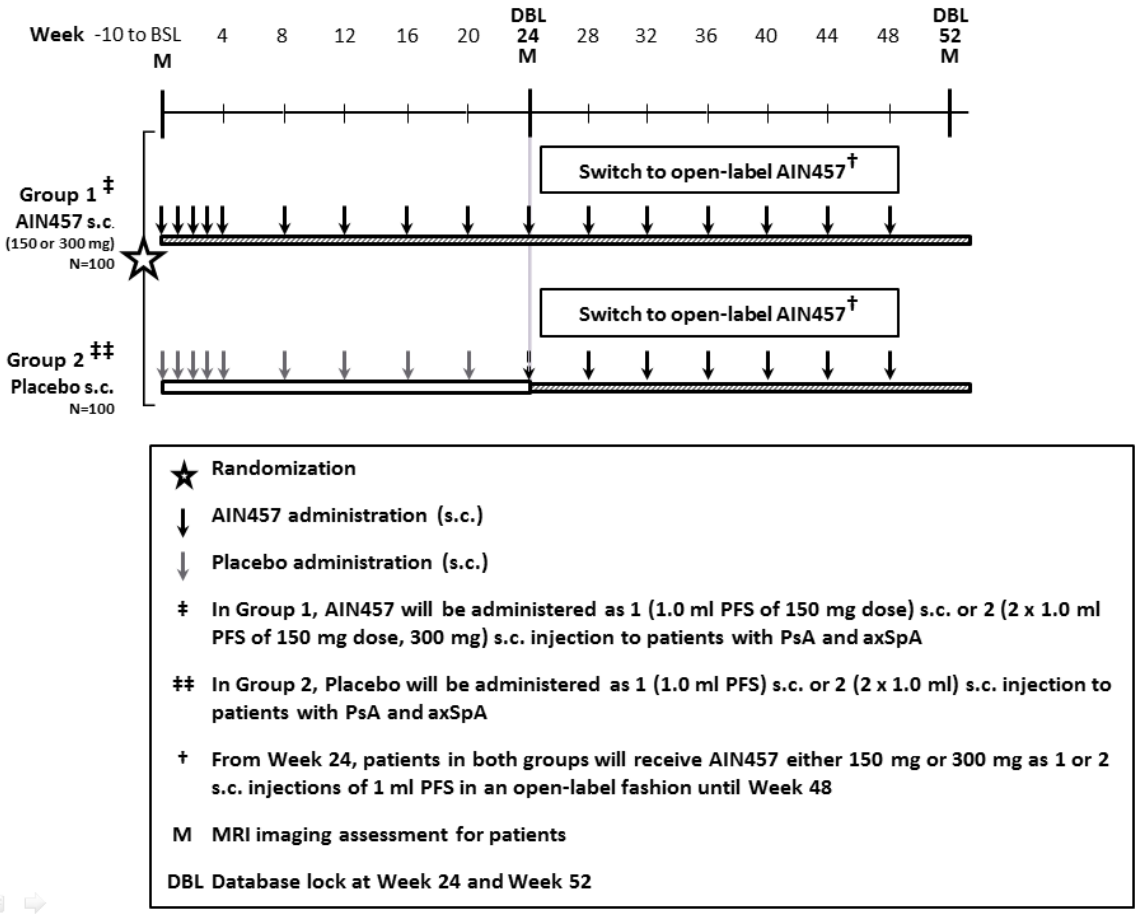
[redacted]

study. If an extension study is agreed on, it will be described in a separate extension study protocol.

Rescue medication will not be allowed before the completion of Week 24 assessments (see Section 5.5.6). Although no patient will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, if rescue with prohibited biologics (as described in Section 5.5.8) occurs prior to completion of Week 24 assessments, patients will be discontinued from the study after an end of study visit (see Table 6-1).

Primary endpoint is the percentage of patients with resolution of Achilles tendon enthesitis as assessed by the respective subcomponent of the LEI at Week 24. Patient-/Physician-reported outcomes and outcome measures of feet MRI imaging performed by central reading will serve as secondary [redacted] endpoints. For patients switched from placebo to secukinumab at Week 24, efficacy assessments at Week 52 will be particularly important.

Figure 3-1 Study design



3.2 Rationale for study design

The double-blind, randomized, parallel-group, placebo-controlled design used in this study up to Week 24 is in alignment with phase III trials of other biologics in this disease area and in compliance with the European Medicines (Evaluation) Agency (EMA/EMEA) guidelines

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(EMA 2005). Placebo group will be re-assigned to active treatment at Week 24. Unblinding of the Novartis Clinical Team will occur after the Week 24 database lock for primary endpoint analysis. Nevertheless all investigators, site personnel, patients, and monitors will continue to remain blinded to the original randomization to active treatment vs. placebo until the Week 52 database lock and analyses are completed so as to ensure reliable efficacy and safety assessments over time. All patients will be on secukinumab treatment from Week 24 up to Week 48. However, data up to 52 weeks is being generated to evaluate the safety and the sustainability of response in this population.

The patient population will be described in more detail in the Section 4 below.

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

The dose (150 mg and 300 mg), dosing regimen (weekly from Baseline to Week 3, monthly from Week 4 to Week 52), formulation (liquid in PFSs) and route of administration (s.c.) of secukinumab used in this study for patients with PsA are in accordance with the approved European SmPC which was supported by the comprehensive PsA (including the pivotal Phase 3 CAIN457F2306 and CAIN457F2312 studies) clinical trial program performed to assess the efficacy, tolerability and safety of secukinumab. For PsA patients in this trial, patients with concomitant moderate to severe psoriasis and patients previously inadequately responding to TNF-α inhibitors will receive 300 mg and all other PsA patients will receive 150 mg secukinumab, according to applicable local regulations.

The dose (150 mg), dosing regimen (weekly from Baseline to Week 3, monthly from Week 4 to Week 52), formulation (liquid in PFSs) and route of administration (s.c.) of secukinumab used in this study for patients with AS are in accordance with the approved European SmPC which was supported by the comprehensive AS (including the pivotal Phase 3 CAIN457F2305 and CAIN457F2310 studies) clinical trial program performed to assess the efficacy, tolerability and safety of secukinumab.

The dose for patients with nr-axSpA (150 mg secukinumab) as well as dosing regimen (weekly from Baseline to Week 3, monthly from Week 4 to Week 52) was chosen in accordance with the ongoing clinical development program for this condition (phase 3 study CAIN457H2315).

The dose (150 mg), dosing regimen (weekly from Baseline to Week 3, monthly from Week 4 to Week 52), formulation (liquid in PFSs) and route of administration (s.c.) of secukinumab used in this study for axSpA patients with objective signs of inflammation at screening, evident by either MRI with Sacroiliac joint inflammation (according to source documentation) and/or hsCRP > ULN (as defined by central lab) is based on the Phase 3 trials in AS, CAIN457F2305 and CAIN457F2310, assessing the efficacy of both 75 mg and 150 mg s.c. maintenance doses with loading regimens consisting of either intravenous doses (CAIN457F2305: 3 doses of 10 mg/kg given every 2 weeks at Baseline, Weeks 2 and 4) or subcutaneous doses (CAIN457F2310: four weekly doses matching the maintenance dose of either 75 mg or 150 mg given at Baseline, Weeks 1, 2, and 3). Given the similarity of the ASAS20 and ASAS 40 response at the Week 16 primary endpoint for the 150 mg dose in each of these studies, regardless of whether the loading dosing was i.v. (CAIN457F2305: 60.8% for IV-150 mg vs 28.7% for placebo for ASAS20 and 41.6% for IV-150 mg vs 13.1% for placebo for ASAS 40) or s.c. (CAIN457F2310: 61.1% for SC-150 mg vs 27.0% for

placebo for ASAS20 and 36.1% for SC-150 mg vs 10.8% for placebo for ASAS 40), secukinumab 150 mg s.c. is a sufficient dose to provide clinically and statistically significant efficacy, whereas higher loading doses of secukinumab do not appear to confer greater efficacy in AS. Of note, the 75 mg s.c. loading and maintenance regimen tested in CAIN457F2310 did not achieve statistically significant improvements in any of the efficacy endpoints tested in a pre-defined testing hierarchy, including ASAS20, ASAS 40, hsCRP, ASAS5/6, BASDAI, SF-36 PCS and ASQoL. Therefore, there are currently no plans to further pursue the 75 mg dose in future axSpA studies. Furthermore, a meta-analysis of trials examining TNF-α inhibitors, demonstrated that nr-axSpA patients respond similarly well to biologic anti-TNF treatments as AS patients (Callhoff et al 2014). There was no evidence that different axSpA populations (e.g. AS and nr-axSpA) could require different dose regimens (Callhoff et al 2014, Landewé et al 2014). As other phase III trials of TNF-α inhibitors in nr-axSpA also evaluated dosages that already proved to be efficacious in AS, this study will use the secukinumab dose of 150 mg s.c. for axSpA patients with objective signs of inflammation at Screening, evident by either MRI with Sacroiliac joint inflammation (according to source documentation) and/or hsCRP > ULN (as defined by central lab).

This study is evaluating the efficacy, including effects on inflammation of secukinumab 150 mg s.c. dose with or without loading regimen and 300 mg s.c. dose with or without loading regimen for the treatment of Achilles tendon enthesitis in patients with active PsA and axSpA.

Data from this study are aimed at broadening secukinumab's profile as a novel treatment option for PsA and axSpA patients with active enthesitis including one Achilles tendon site.

This study employs active secukinumab treatment groups with:

- Loading regimen at 150 mg s.c. administered at Baseline, Weeks 1, 2 and 3, followed by a maintenance regimen of 150 mg s.c. every 4 weeks starting at Week 4.
- Loading regimen at 300 mg s.c. administered at Baseline, Weeks 1, 2 and 3, followed by a maintenance regimen of 300 mg s.c. every 4 weeks starting at Week 4.
- No load regimen of doses of 150 mg s.c. or 300 mg s.c. administered every 4 weeks in placebo group starting at Week 24.

The loading regimen is supported by model-based analyses using data from psoriasis studies, predicting significantly improved psoriasis area and severity index 75 response rate after 12 weeks of treatment, compared to the response rates with monthly dosing. A loading regimen with 4 weekly doses of either 150 mg s.c. or 300 mg s.c. is expected to sustain rapid onset and greater magnitude of the effect of secukinumab on resolution of Achilles tendon enthesitis in patients with PsA and axSpA. The loading regimen with 4 weekly doses of either 150 mg s.c. or 300 mg s.c. is also expected to have a rapid and improved effect on the inhibition of inflammation and structural damage. The approach for the no-load regimen has also been employed in this study in placebo group starting at Week 24 to investigate the onset and sustainability of efficacy of secukinumab 150 mg s.c. and 300 mg s.c. administered every 4 weeks in patients with PsA and axSpA. Assessment of joint and/or bone structure preservation is planned to be assessed using MRI scan.

Duration of treatment for up to 1 year has been chosen since Achilles tendon enthesitis needs comparably more time to resolve than other PsA and axSpA manifestations especially with regards to structural preservation. In the "Heel" trial no significant changes in MRI parameters

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could be observed at Week 12 (Dougados et al 2010). Placebo patients who switch at Week 24 would thereby be on active treatment for 6 months.

3.4 Rationale for choice of comparator

A placebo group is included in this study up to Week 24. Due to the nature of the disease and the primary outcome measure used (percentage of patients with resolution of Achilles tendon enthesitis as assessed by the respective subcomponent of the LEI), 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 24 weeks. The continuation of the placebo group up to Week 24 can be supported from an ethical standpoint. Firstly, patients can continue on 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 Food and Drug Administration (FDA) 1999/EMA 2006, and the parallel-group, placebo-controlled design is in alignment with phase III trials of other biologics in this therapeutic domain as outlined in EMA guidelines (EMA 2006).

3.5 Purpose and timing of interim analyses/design adaptations

The primary endpoint analysis will be performed after all patients have completed the visit associated with the primary endpoint (Week 24). The interpretation of the MRI data will be performed by an imaging service provider and readers will be blinded to the treatment as well as visit information. The final analysis will be conducted after all patients have completed the study (Week 52). Additional analyses may be performed to support interactions with health authorities, as necessary.

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) 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.

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, RA, AS, PsA, multiple sclerosis and uveitis). Overall secukinumab was generally safe and well-tolerated.

The risk profile of secukinumab in AS and PsA 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

[redacted]

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. No new or unexpected safety signals were detected in any AS and PsA study for any dose regimen and the safety profile in this patient population was consistent with the safety profile observed in other indications including psoriasis.

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 brochure (IB).

4 Population

The study population will consist of male and female patients (≥ 18 years old at the time of consent) with active PsA or axSpA presenting active enthesitis including one Achilles tendon site that is refractory to standard treatment as defined in Section 4.1 and Section 4.2.

4.1 Inclusion criteria

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

1. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must provide written, signed and dated informed consent before any study assessment is performed.
2. Male or non-pregnant, non-lactating female patients at least 18 years of age.
3. PsA patients must fulfill the following criteria:
   - Diagnosis of PsA classified by CASPAR criteria with symptoms for at least 6 months (Appendix 3) **and**
   - Active PsA as assessed by ≥ 1 tender joints out of 78 and ≥ 1 swollen joints out of 76 at Baseline (dactylitis of a digit counts as 1 joint each).
4. AxSpA patients must fulfill the following criteria:
   - AxSpA as per the classification of the ASAS axial SpA criteria (Appendix 4) with objective signs of inflammation at screening, evident by either MRI with Sacroiliac joint inflammation or definite radiographic sacroilitis according to the modified New York criteria (Appendix 5) (both according to source documentation) and/or hsCRP > ULN (as defined by central lab) **and**
   - Active disease assessed by total BASDAI ≥ 4 (0-10) (Appendix 6) at Baseline.
5. Diagnosis of Achilles tendon enthesitis according to swelling and tenderness at the insertional site of the Achilles tendon into the calcaneus.
6. Onset of heel pain ≥ 1 month at Baseline.
7. Heel enthesitis that is MRI-positive according to the investigator`s judgement.
8. The heel enthesitis must have been refractory to standard treatment defined as either NSAIDs for at least 1 month at the maximal recommended or tolerated dose unless withdrawal because of intolerance, toxicity or contraindications or TNF-inhibitors as described in inclusion criterion 16.
9. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies negative at Screening.
10. Patients should have been on NSAIDs at the highest recommended dose for at least 1 month prior to randomization with an inadequate response or failure to respond, or less if

therapy had to be withdrawn due to intolerance, toxicity or contraindications or on TNF-inhibitors as described in inclusion criterion 16.

11. Patients who are regularly taking NSAIDs as part of their PsA or axSpA therapy are required to be on a stable dose for at least 2 weeks before study randomization and should remain on a stable dose up to Week 24.
12. Patients taking corticosteroids must be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization and should remain on a stable dose up to Week 24.
13. Patients taking MTX (7.5 mg/week to 25 mg/week) or - only in case of axSpA - sulfasalazine (≤ 3 g/day) are allowed to continue their medication and must have taken it for at least 3 months and have to be on a stable dose for at least 4 weeks prior to randomization and should remain on a stable dose up to Week 24.
14. Patients on MTX must be on folic acid supplementation at randomization.
15. Patients who are on a DMARD other than MTX or - only in case of axSpA - sulfasalazine must discontinue the DMARD 4 weeks prior to randomization, except for leflunomide, which has to be discontinued for 8 weeks prior to randomization unless a cholestyramine washout has been performed.
16. Patients who have been on a TNFα inhibitor (not more than two) must have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months prior to randomization or have been intolerant to at least one administration of an anti-TNFα agent
17. Patients who have previously been on a TNFα inhibitor will be allowed entry into study after an appropriate wash-out period prior to randomization:
    - 4 weeks for etanercept – with a terminal half-life of 102 ± 30 hours (s.c. route)
    - 8 weeks for infliximab – with a terminal half-life of 8.0-9.5 days (i.v. infusion)
    - 10 weeks for adalimumab – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route)
    - 10 weeks for Simponi® (golimumab) – with a terminal half-life of 11-14 days
    - 10 weeks for Cimzia® (certolizumab) – with a terminal half-life of 14 days

4.2 Exclusion criteria

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

1. Chest X-ray or 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. Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor.
4. 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.
5. Ongoing use of psoriasis treatments / medications (e.g. topical corticosteroids, UV therapy) at randomization. The following wash out periods need to be observed:

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- Oral or topical retinoids: 4 weeks.
- Photochemotherapy (e.g. PUVA): 4 weeks.
- Phototherapy (UVA or UVB): 2 weeks.
- Topical skin treatments (except in face, eyes, scalp and genital area during screening, only corticosteroids with mild to moderate potency): 2 weeks.

6. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.
7. Any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization.
8. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization.
9. Patients who have previously been exposed to more than two (2) TNF inhibitors (investigational or approved).
10. Patients who have ever received biologic immunomodulating agents, except those targeting TNFα.
11. 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).
12. 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.
13. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and minimum 16 weeks or longer if local label requires it (e.g. 20 weeks in EU) after stopping the study medication. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least 6 weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository.
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

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

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

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appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

14. Active ongoing inflammatory diseases other than PsA and axSpA that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease or uveitis.
15. 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.
16. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥ 160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV), and uncontrolled diabetes.
17. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFT) such as aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/ serum glutamic pyruvic transaminase (ALT/SGPT), alkaline phosphatase, or serum bilirubin. The investigator should be guided by the following criteria:
    - Any single parameter may not exceed 2 × ULN. A single parameter elevated up to and including 2 × ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out laboratory error.
    - If the total bilirubin concentration is increased above 2 × ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed the value of 1.6 mg/dL (27 μmol/L).
18. 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).
19. Screening total white blood cell (WBC) count < 3000/μL, or platelets < 100000/μL or neutrophils < 1,500/μL or hemoglobin < 8.5 g/dL (85 g/L).
20. Active systemic infections during the last 2 weeks (exception: common cold) prior to randomization.
21. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by a positive QuantiFERON TB-Gold test. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated.
22. Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening or randomization.
23. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).

24. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial.
25. Inability or unwillingness to undergo repeated venipuncture (e.g. because of poor tolerability or lack of access to veins).
26. 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.
27. Donation or loss of 400 mL or more of blood within 8 weeks before randomization.
28. History or evidence of ongoing alcohol or drug abuse, within the last 6 months before randomization.
29. Plans for administration of live vaccines during the study period or within 6 weeks preceding randomization.
30. Inability or unwillingness to undergo MRI of the feet (e.g., patients with pacemakers, or metal fragments / foreign objects in the body that are not compatible with performing an MRI of the feet)

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Novartis will supply the following:

- Study treatment:
  Secukinumab 150 mg provided in 1 ml PFS.
- Placebo:
  Secukinumab placebo provided in a 1 ml PFS.

The PFSs are packed in a double blinded fashion and do not need to be prepared. The study treatments will be labeled as follows:

- Double-blind secukinumab and placebo PFS will be labeled as AIN457 150 mg/1ml/Placebo for dosing till Week 24.
- Open-label secukinumab PFS will be labeled as AIN457 150 mg/1ml.

Note: The secukinumab PFSs are packed in double-blinded fashion until Week 24 when open-label treatment is started and, therefore, do not need to be prepared by the study site. Starting at Week 24, open-label medication will be supplied until the last dose is given at Week 48.

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

5.1.2 Additional treatment

No additional treatment beyond study drug and control drug are included in this trial.

5.2 Treatment arms

Patients will be randomized to one of the following 2 treatment groups in a 1:1 ratio as depicted below:

[redacted]

- Group 1: secukinumab 150 mg/300 mg s.c.: secukinumab as 1 (1.0 mL PFS of 150 mg dose) s.c. or 2 (2 × 1.0 mL PFS of 150 mg dose, 300 mg) s.c. injections at Baseline, Weeks 1, 2, and 3, followed by administration every 4 weeks starting at Week 4.
  - PsA patients, who have been previously exposed to TNF blockers, and/or with concomitant moderate to severe plaque psoriasis receive 2 (two) 1.0 mL PFS of 150 mg dose (i.e. 300 mg) s.c..
  - Other PsA patients and axSpA patients receive 1 (one) 1.0 mL PFS of 150 mg dose s.c..
- Group 2: placebo s.c. followed by secukinumab 150 mg/300 mg s.c. at Baseline, Weeks 1, 2, and 3, followed by administration every 4 weeks starting at Week 4.2
  - PsA patients, who have been previously exposed to TNF blockers, and/or with concomitant moderate to severe plaque psoriasis receive placebo as 2 (two) 1.0 mL PFS s.c..
  - Other PsA patients and axSpA patients receive placebo as 1 (one) 1.0 mL PFS s.c..

  At Week 24, all patients in Group 2 will switch to their pre-assigned secukinumab treatment

Patients will receive study treatment at Baseline, Weeks 1, 2, and 3, followed by treatment every 4 weeks through Week 52 (last dose given at Week 48). At Week 24, patients originally randomized to placebo will switch to receive secukinumab 150 mg (1 injection of secukinumab 1 mL/150 mg) or secukinumab 300 mg (2 injections of secukinumab 1 mL/150 mg) in open-label fashion without a loading regimen. Blinding to the original treatment assignment will be maintained until after the Week 52 database lock and analyses are completed (see Section 5.4). Patients will self-administer all secukinumab and placebo doses as described in Section 3.1 at the study site or at home at indicated study visits (see Table 6-1) through Week 52.

5.3 Treatment assignment and randomization

At Baseline, all eligible patients will be randomized via Interactive Response Technology (IRT) to 1 of the 2 treatment arms 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, 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 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).

Patients will be stratified at randomization on the basis of PsA or axSpA disease. Based on enrollment target, it is planned that approximately 50% of randomized patients should be PsA

and approximately 50% axSpA patients to ensure a balanced patient population for the assessment of efficacy and safety.

Additionally, it is planned to enroll no more than 40% TNF-IR patients in the study.

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

5.4 Treatment blinding

Patients, investigator staff and persons performing the assessments remain blinded to the identity of the treatment from the time of randomization until Week 52 database lock, using the following methods:

- Up until the Week 52 database lock and analyses are completed, all original randomized treatment assignments will be double-blinded to patients, investigators, and site personnel.
- Following the Week 24 database lock, the Sponsor will be unblinded to treatment assignment.
- After the Week 52 database lock and analyses have been completed, site personnel and patients may be unblinded to the original randomized treatment assignment at Baseline.

The identity of the original randomized treatments administered through Week 24 will be concealed up to the Week 52 database lock and analyses are completed by the use of study treatments in the form of PFS that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Patients will be instructed by site staff on how to self-administer the s.c. injection using the PFS containing the liquid formulation of secukinumab, based on the Instructions for Use (IFU). The study drug will be administered by the patient into the appropriate injection site of the body s.c. under the supervision of the site staff. All injections through Week 52 will be performed at the study site or at home (see Table 6-1).

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9), at the time of the interim analysis (see Section 9.7) and at the conclusion of the study.

The hsCRP results from samples collected during the treatment period will be revealed to everyone involved in the study only after the Week 52 database lock and analyses are completed.

As a primary efficacy analysis will be performed at Week 24, there will be a database lock when all patients have completed Week 24 assessments. 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 52 week study.

5.5 Treating the patient

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

5.5.1 Patient numbering

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

[redacted]

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

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

Patients may be re-screened once and will receive a new Patient Number after they have been re-consented. Patients who are mis-randomized cannot be re-screened; mis-randomization occurs when a patient who does not meet all eligibility criteria receives a randomization number incorrectly.

5.5.2 Dispensing the study drug

Each study site will be supplied with study treatment for secukinumab/placebo in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique randomization number is printed on each part of this label which corresponds to 1 of the 2 treatment groups. Investigator staff will identify the study treatment packages to dispense to the patient by contacting the IRT and obtaining the medication numbers. Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Pharma Organization Quality Assurance.

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

The PFS (150 mg active/placebo) sealed in an outer box must be stored in a access controlled/locked refrigerator between 2°C and 8°C (36°F and 46°F) and protected from light. They must be carefully controlled in accordance with regulations governing study medicinal products and local regulations.

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

[redacted]

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

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Study treatment (150 mg secukinumab and placebo) will be administered by s.c. PFSs throughout the study. Administration of study treatment will occur at the study site or at home from Baseline up to Week 52.

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

The PFS with the ready-to-use study treatment solution will be provided by the site staff to the patient. Detailed instructions on the self-administration of the study treatment will be described in IFU and provided to each patient. At the Baseline visit, patients will be instructed by the site staff, utilizing the IFU, on how to self-inject using a PFS. Patients will be asked to raise questions, if they have any, and then to proceed with self-injection. The first study treatment administration will occur at the Baseline visit only after eligibility criteria have been confirmed, all study scheduled Baseline assessments have been performed and the scheduled blood samples have been drawn.

At the Week 1 visit, patients will be asked to refer to the IFU and to proceed directly with self-injection of the study drug (i.e. no prior retraining) for the remainder of the trial. However, if the patient is not comfortable self-injecting the study treatment, then the site staff or caretaker may administer it for the patient.

At each subsequent visit, all study assessments, including the completion of patient-reported outcomes (as applicable per Table 6-1), should be completed prior to the self-injection of study treatment.

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

Subcutaneous administration with pre-filled syringes

Secukinumab solution for subcutaneous injection (150 mg in 1.0 mL active/placebo) will be provided in PFSs.

The study treatment solution must be injected into non-affected areas of the skin.

Patients will be instructed by the site staff on how to self-inject study treatment using a PFS, following the IFU. The injections will be self-administered into the appropriate site of the body (thighs, arms, abdomen), and each injection should be given at a different injection site to reduce the risk of reaction. Each new injection should be given at least 1 inch from the previously used site. If patient chooses the abdomen, a 2 inch area around the navel should be

[redacted]

avoided. Study drug should not be injected into areas where the skin is tender, bruised, red, or hard, or where patient has scars or stretch marks.

Single PFSs will be packaged in individual boxes. The boxes containing the PFSs with study treatment solution should be kept at 2°C to 8°C (36°F and 46°F) (Do Not Freeze) and protected from light. Prior to administration the boxes containing the PFSs with study treatment solution should be allowed to come to room temperature **unopened** for 15 minutes-30 minutes prior to injection. Used PFSs should be disposed immediately after use in a sharps container OR according to the regulatory needs of the respective countries.

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

Home administration

Up to Week 24, all doses of study treatment will be self-administered by the patient at the study site, after the study assessments for the visit have been completed. After Week 24, the patients will be allowed to self-administer the study treatment at home during the optional visits in which there are no scheduled site assessments. Optional site visits are included in the assessment table for Treatment Period 2 of the study (Table 6-1) and between visits in which trial-related procedures are to be conducted. Patients will be allowed to self-administer the study treatment via PFS at home or to visit the site during the optional visits to self-administer study treatment under the supervision of the site staff. If the patient opts for home administration of study treatment and is unable or unwilling to self-administer the treatment via PFS, a caregiver may administer the study treatment after Week 24 during Treatment Period 2 only. Caregivers should be trained on the IFU prior to administering the study treatment to the patient. Information about self-administration i.e. whether the patient self-administered the study treatment at home or at the site and if a caregiver administered the treatment should be recorded on the Dose Administration Record eCRF. Prior to self-administration at home, patients should contact the investigator/site staff in case they are experiencing any AE/SAEs, or have any concerns. All dates and times of self-administrations by the patient during the study must be recorded on the Dosage Administration Record eCRF. Immediately before dispensing the package to the patient, site staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

5.5.5 Permitted dose adjustments and interruptions of study treatment

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

[redacted]

Study treatment 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 Dosage Administration Record CRF.

5.5.6 Rescue medication

Rescue medication is defined as medication used to control symptoms that are not adequately controlled on study treatment.

Rescue medication must not be used before completion of Week 24 assessments as previously outlined in Section 3.1. Please see Section 5.5.7 and Section 5.5.8 for details on concomitant and prohibited medication for this study. Although no patient will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, if rescue with prohibited treatments (as described in Section 5.5.8) occurs prior to completion of Week 24 assessments, patients will be discontinued from the study.

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

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.

Changes in NSAIDs concomitant therapy is permitted after Week 24 assessments as per the investigator's clinical judgment.

Patients taking MTX (7.5 mg/week to 25 mg/week) or sulfasalazine (only in case of axSpA, $\leq$ 3 g/day) are allowed to continue their medication and must have taken it for at least 3 months and have to be on a stable dose for at least 4 weeks prior to randomization and should remain on a stable dose up to Week 24. Any changes in dose or initiation after Week 24 must be recorded in the Concomitant medications eCRF page.

After Week 24, the dose and regimen of other concomitant medications may be adjusted slowly at the investigator's discretion and recorded appropriately on the Concomitant medications eCRF page.

5.5.7 Concomitant medication

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

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

[redacted]

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

Guidelines for the use of specific medications are provided below:

Methotrexate

Patients taking MTX (up to 25 mg/week) must be on a stable dose for at least 4 weeks before randomization and maintained stable until Week 24.

Folic acid

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

Sulfasalazine

Patients taking sulfasalazine (≤ 3 g/day) must be on a stable dose for at least 4 weeks before randomization and maintained stable until Week 24. Any changes in dose or initiation after Week 24 must be recorded in the Prior/Concomitant medications eCRF page.

Leflunomide wash-out with cholestyramine

In case of leflunomide treatment, a drug wash-out of 8 weeks has to be performed. However, another wash-out procedure might be considered. Cholestyramine could be given orally to wash-out the drug at a dose of 8 g t.i.d. Cholestyramine has been shown to reduce plasma levels of the active leflunomide metabolite by approximately 40% in 24 hours and by 49% to 65% in 48 hours in 3 healthy volunteers. The administration of cholestyramine is recommended in patients who require a drug elimination procedure. If a patient receives 8 g t.i.d. for 11 days he/she could be safely randomized 4 weeks after the beginning of the 11-day treatment period.

Systemic corticosteroids

Treatment with systemic corticosteroids is permitted up to a maximum daily dosage of ≤ 10 mg prednisone equivalent and if the dose was stable within the 2 weeks preceding randomization. The patient should remain on a stable dose until Week 24.

Corticosteroid dose reductions below 10 mg prednisone equivalent are permitted after Week 24 although the corticosteroid dose should not be reduced more than 1 mg prednisone equivalent every 4 weeks.

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

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

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

[redacted]

Patients should have been on NSAIDs at the highest recommended dose for at least 1 month prior to randomization with an inadequate response or failure to respond, or less if therapy had to be withdrawn due to intolerance, toxicity or contraindications.

Patients regularly using NSAIDs, low strength opioids, or paracetamol/acetaminophen should be on stable dose for at least 2 weeks before randomization to allow inclusion. They should remain on a stable dose in the study up to Week 24. However, they have to refrain from any intake during at least 24 hours before a visit with disease activity assessment.

After Week 24 assessments are completed, a change in the NSAIDs, low strength opioids, or paracetamol/acetaminophen treatment regimen as well as PRN use are permitted.

Any change of the NSAIDs, low strength opioids, or paracetamol/acetaminophen treatment during the trial should be recorded in the Prior/Concomitant medications eCRF page.

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-1 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 5-1 Prohibited medication

Prohibited medication	Washout period (before randomization)
Etanercept*	4 weeks
Infliximab*	8 weeks
Adalimumab, golimumab, certolizumab*	10 weeks
Biological immunomodulating agents* except TNF inhibitors as described above	Never
Unstable dose of MTX or sulfasalazine (until Week 24)	4 weeks
Other DMARD (incl. apremilast, except MTX and – in case of axSpA - sulfasalazine)	4 weeks
Leflunomide	8 weeks
Leflunomide with cholestyramine washout	4 weeks
Unstable doses of NSAIDs (COX1 or COX2 inhibitors), low strength opioids, paracetamol/acetaminophen (until Week 24). After week 24, use PRN is allowed.	2 weeks
Analgesics, other than NSAIDs or paracetamol/acetaminophen or low strength opioids as described above	2 weeks
Systemic corticosteroids > 10 mg prednisone equivalent** (until Week 52)	2 weeks
Unstable dose of systemic corticosteroids ≤ 10 mg prednisone equivalent (until Week 24)	2 weeks
Intra-articular injections (until Week 24)	4 weeks
Intramuscular or intravenous corticosteroid treatment	4 weeks
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)	Never
Any investigational treatment or participation in any interventional Trial	4 weeks or 5 half-lives (whichever is longer)

[redacted]

Prohibited medication	Washout period (before randomization)
Live vaccines (and until 12 weeks after last study treatment administration, see above)	6 weeks
Oral or topical retinoids	4 weeks
Photochemotherapy (e.g. PUVA)	4 weeks
Phototherapy (UVA or UVB)	2 weeks
Topical skin treatments (except in face, eyes, scalp and genital area during screening, only corticosteroids with mild to moderate potency)	2 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); PUVA = psoralen and ultraviolet A; UVA = ultraviolet A; UVB = ultraviolet B: TNF = tumor necrosis factor.

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

** See details about corticosteroid management in Section 5.5.7.

5.5.9 Emergency breaking of assigned treatment code

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

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

- protocol number
- study drug name (if available)
- patient number

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

Study drug must be discontinued after emergency unblinding.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol i.e. Visit 18/Week 52 (see Table 6-1).

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

[redacted]

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

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

nr-axSpA patients with objective signs of inflammation at Screening, evident by either MRI with sacroiliac joint inflammation (according to source documentation) and/or hsCRP > ULN (as defined by central lab) who successfully complete the 1 year trial duration and were benefiting from secukinumab 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
- Emergence of the following AEs:
  - Any severe 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 on balance, he/she thinks that continuation would be detrimental to the patient's well-being. While PsA and axSpA are multifaceted diseases and the assessment of responder status should be based on the global clinical picture and not on a single efficacy parameter; not achieving an improvement (e.g. in the TJC or SJC

[redacted]

of ≥ 20% [PsA patients]) or BASDAI of ≥ 20% or ≥ 1 unit (0-10 scale) (axSpA patients, Pavy et al 2005) at Week 36 may be considered as a guidance for considering a patient inadequate responder to secukinumab treatment.

For patients who discontinue study treatment, a Dosage Administration Record eCRF 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.

Patients who prematurely discontinue during Treatment Period 1 (secukinumab/placebo treatment from Baseline through Week 24) should return for assessments associated with Week 24 visit (4 weeks after the last study treatment in Treatment Period 1). Patients who prematurely discontinue during Treatment Period 2 (secukinumab treatment from Week 24 through Week 52) should return and complete assessments associated with Week 52 visit (4 weeks after the last study treatment in Treatment Period 2, see Table 6-1). 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

- 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 the assessment Table 6.1 below.

[redacted]

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 period of the study from Screening to Week 52 (Treatment Periods 1 and 2), the assessments must be performed as indicated in Table 6-1.

Preferably, patients should be seen for all visits on the designated day, or within the recommended visit window to the original planned visit.

- For visits scheduled through Week 4, the study treatment should not be administered less than 7 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.

Recommended visit windows:

- ± 2 days for Baseline, Week 1, Week 2, Week 3 and Week 4, Week 24 and Week 52
- ± 2 days for all study drug home administrations
- ± 5 days for all other study visits

Patients who prematurely discontinue during a specific treatment period should return for the final visit within that treatment period (4 weeks after the last study treatment administration). At this final visit, all dispensed study product should be reconciled with the source documents including the AE and concomitant medications reconciled on the eCRF.

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 informed consent form (ICF). Once patient signs the ICF, he will be screened for eligibility criteria. Screening will be

[redacted]

flexible in duration based on the time required to washout prior antirheumatic and other medications and will have a duration of up to 8 weeks (see Section 5.5.5). During Screening Visit, initial assessments will be performed as outlined in Table 6-1. At that visit (Screening), the duration of the washout period will be determined.

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.

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

	Screening	Treatment Period 1										Treatment Period 2							Unscheduled visit[a]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Week	**≤ -10**	**BSL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24*** TD/PPD	**28**	**32**	**36**	**40**	**44**	**48**	**52*** TD/PPD	
Day	**≤ -70**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	
Recommended visit window (± days)		**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 5**	**± 5**	**± 5**	**± 2**	**± 2**	**± 2**	**± 5**	**± 2**	**± 2**	**± 2**	**± 2**	
Optional site visit because of home administration												X	X		X	X	X		
Administration of s.c. study treatment via PFS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Obtain informed consent	X																		
Inclusion & Exclusion criteria[b]	X	X																	
Hepatitis B, C or HIV serology (only in countries where it is required)[c]	S																		
Relevant medical history/current medical condition	X																		
Washout evaluation/ instruction	S																		
Smoking history	X																		
Cardiovascular medical	X																		

[redacted]

	Screening	Treatment Period 1										Treatment Period 2							Unscheduled visit[a]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Week	**≤ -10**	**BSL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24*** TD/PPD	**28**	**32**	**36**	**40**	**44**	**48**	**52*** TD/PPD	
Day	**≤ -70**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	
Recommended visit window (± days)		**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 5**	**± 5**	**± 5**	**± 2**	**± 2**	**± 2**	**± 5**	**± 2**	**± 2**	**± 2**	**± 2**	
history																			
Demography	X																		
PsA/axSpA medical history and previous therapies	X																		
Physical exam	S	S					S		S		S			S				S	S
Height	X																		
Weight	X																		
Vital signs[d]	X	X		S		S	X	S	X	S	X			X				X	X
QuantiFERON TB-Gold test	X																		X
Chest X-ray/MRI[e]	S																		
Serum pregnancy test	X																		X
Urine pregnancy test		X				X	X	X	X	X	X	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X
Rheumatoid factor	X																		
Anti-CCP	X																		
Electrocardiogram[g]		X																X	X

[redacted]

	Screening	Treatment Period 1										Treatment Period 2							Unscheduled visit[a]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Week	**≤ -10**	**BSL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24*** TD/PPD	**28**	**32**	**36**	**40**	**44**	**48**	**52*** TD/PPD	
Day	**≤ -70**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	
Recommended visit window (± days)		**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 5**	**± 5**	**± 5**	**± 2**	**± 2**	**± 2**	**± 5**	**± 2**	**± 2**	**± 2**	**± 2**	
Randomization via IRT		X																	
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	X	X	X	X	
Assessments only in PsA patients																			
CASPAR criteria	X																		
[redacted]																			
Assessments only in axSpA patients																			
ASAS criteria/modified New York criteria[h]	X																		
[redacted]																			

[redacted]

	Screening	Treatment Period 1										Treatment Period 2							Unscheduled visit[a]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Week	**≤ -10**	**BSL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24*** TD/PPD	**28**	**32**	**36**	**40**	**44**	**48**	**52*** TD/PPD	
Day	**≤ -70**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	
Recommended visit window (± days)		**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 5**	**± 5**	**± 5**	**± 2**	**± 2**	**± 2**	**± 5**	**± 2**	**± 2**	**± 2**	**± 2**	
Assessments for all patients																			
Heel pain		X	X	X	X	X	X	X	X	X	X			X				X	X
MRI of the affected foot	X										X							X	X
Prior/Concomitant medication/non-drug therapy	X	X	X	X	X	X	X	X	X	X	X	X[i]	X[i]	X	X[i]	X[i]	X[i]	X	X
AEs/SAEs[j] (including injection site reactions)	X	X	X	X	X	X	X	X	X	X	X	X[k]	X[k]	X	X[k]	X[k]	X[k]	X	X
LEI	X	X	X	X	X	X	X	X	X	X	X			X				X	X
Patient's assessment of heel enthesiopathy activity		X	X	X	X	X	X	X	X	X	X			X				X	X
Physician's assessment of heel enthesiopathy activity		X	X	X	X	X	X	X	X	X	X			X				X	X
Patient's global assessment of disease activity		X	X	X	X	X	X	X	X	X	X			X				X	X
Physician`s global assessment of		X	X	X	X	X	X	X	X	X	X			X				X	X

[redacted]

	Screening	Treatment Period 1										Treatment Period 2							Unscheduled visit[a]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Week	**≤ -10**	**BSL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24*** TD/PPD	**28**	**32**	**36**	**40**	**44**	**48**	**52*** TD/PPD	
Day	**≤ -70**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	
Recommended visit window (± days)		**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 5**	**± 5**	**± 5**	**± 2**	**± 2**	**± 2**	**± 5**	**± 2**	**± 2**	**± 2**	**± 2**	
disease activity																			
SF-36 v2		X	X	X	X	X	X	X	X	X	X			X				X	X
[redacted]																			
Hematology, blood chemistry, urinalysis[m]	X	X		X		X	X	X	X	X	X			X				X	X
HLA-B27	X																		
Treatment period 1 completion form											X								
Treatment period 2 completion form																		X	

X = assessment to be recorded on clinical database.

S = assessment to be recorded on source documentation only.

* Patients who prematurely discontinue during Treatment Period 1 should return for assessments associated with Week 24 visit (4 weeks after the last study treatment in Treatment Period 1). Patients who prematurely discontinue during Treatment Period 2 should return and complete assessments associated with Week 52 visit (4 weeks after the last study treatment in Treatment Period 2).

[a] Unscheduled visit – assessments at discretion of the investigator.

[b] Eligibility assessments are conducted at Screening and at BSL. The data for both visits should be recorded on the corresponding eSource/eCRF available at SV.

[redacted]

[C] Tests performed during screening period only if required as per local regulators prior to initiation of therapy.

[d] For Vitals, blood pressure will be measured 3 times and its mean will be analyzed.

[e] 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

[f] For home administration test kits will be provided by central lab and test will be performed at home.

[g] Clinically relevant abnormalities should be recorded on the relevant medical history/Current medical conditions eCRF page for the Baseline ECG. Clinically relevant abnormalities noted after the Baseline ECG should be reported as AEs on the Adverse Event eCRF page.

[h] The following eCRFs are to be completed: axSpA disease background eCRF, modified New York criteria for AS eCRF and history of extra-axial involvement eCRF (Extra-axial involvement such as uveitis, psoriasis, inflammatory bowel disease, dactylitis, enthesitis, peripheral arthritis).

[i] Update as necessary

[j] 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 84 days after the patient has stopped study participation (whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

[K] Update as necessary

[redacted]

[m] Kits for urinalysis will be provided by central lab and test is performed locally.

AE = adverse event, Anti-CCP = anti-cyclic citrullinated peptide, ASAS=assessment of spondyloarthritis international society, axPsA =axial psoriatic arthritis (i.e. psoriatic arthritis with axial involvement), [redacted], BSL = baseline, CASPAR=classification criteria for psoriatic arthritis, [redacted], HLA-B27 = human leukocyte antigen B27, [redacted], IRT= interactive response technology, LEI = leeds enthesitis index, MRI = magnetic resonance imaging, PFS = prefilled syringe, PPD = premature patient discontinuation, RF = rheumatoid factor, SAE = serious adverse event, SF-36 v2 = medical outcome short form (36) health survey, TD = treatment discontinuation, VAS = visual analog scale.

[redacted]

6.1 Information to be collected on screening failures

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

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

Adverse events that are not serious will be followed by the investigator and collected only in the source data.

All patients who have signed informed consent and are randomized into the Treatment Period 1 of the study will have all AEs **occurring after informed consent is signed** recorded in the Adverse Event eCRF.

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

6.2 Patient demographics/other baseline characteristics

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

- Date of birth, age, sex, race, and source of patient referral.
- Relevant PsA/axSpA and general medical history/current medical condition data until the ICF is signed, such as date of diagnosis of PsA/axSpA, previous PsA/axSpA therapies, AS/axSpA functional status, history of extra-axial involvement (uveitis, psoriasis, inflammatory bowel disease, dactylitis, enthesitis, peripheral arthritis), date of onset of inflammatory back pain, number of previous DMARDs used, cardiovascular medical history, smoking history and surgical sterilization for females if applicable.

Whenever possible, diagnoses and not symptoms will be recorded.

6.3 Treatment exposure and compliance

All dates and times of study treatment administration will be recorded in the appropriate eCRF page.

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

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

[redacted]

6.4 Efficacy

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

- Assessments in all patients:
  - Resolution of Achilles tendon enthesitis as assessed by the respective subcomponent of the Leeds enthesitis index (LEI).
  - Enthesitis assessment (LEI).
  - Heel pain (NRS).
  - Physician`s global assessment of disease activity (VAS).
  - Patient's global assessment of disease activity (VAS).
  - Physician`s global assessment of heel enthesiopathy activity (VAS).
  - Patient's global assessment of heel enthesiopathy activity (VAS).
  - Magnetic Resonance Imaging (MRI) including subcomponents of the Psoriatic arthritis magnetic resonance imaging scoring system (PsAMRIS).

[redacted]

Details relating to the administration of all PROs are provided in Appendix 8.

6.4.1 Assessments in all patients

6.4.1.1 Enthesitis assessment

The LEI is a validated enthesitis index that uses 6 sites for evaluation of enthesitis: lateral epicondyle humerus L + R, proximal Achilles L + R and medial condyle femur L + R. Tenderness on examination is recorded as either present (1) or absent (0) for each of the 6 sites, for an overall score range of 0–6. Higher count represents greater enthesitis burden.

The LEI demonstrated substantial to excellent agreement with other scores in the indication of PsA (Healy and Helliwell 2008) and axSpA (Landewé and van Tubergen 2015).

Resolution of Achilles tendon enthesitis

Resolution of Achilles tendon enthesitis will be assessed by the respective subcomponent of the LEI.

[redacted]

6.4.1.2 Heel pain

The patient's assessment of heel pain will be performed using a 10-point numeric rating scale (NRS) ranging from 'no pain' to 'unbearable pain' after the question '*Please indicate with a cross (X) at the respective number the most pain you had from your heel today'*.

6.4.1.3 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.

6.4.1.4 Patient's global assessment of disease activity

The patient's global assessment of disease activity will be performed using a 100 mm VAS ranging from 'not severe ' to 'very severe ' after the question '*How active was your disease on average during the last week? , Please indicate your response with a vertical mark (|) through the horizontal line.'*

6.4.1.5 Physician's global assessment of heel enthesiopathy activity

The physician`s global assessment of heel enthesiopathy activity will be performed using 100 mm VAS ranging from no activity to maximal activity, after the question *'Considering all the ways the heel enthesitis 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 heel enthesiopathy activity, when performing his own assessment on that patient.

6.4.1.6 Patient's global assessment of heel enthesiopathy activity

The patient's global assessment of heel enthesiopathy activity will be performed using a 100 mm VAS ranging from 'not severe' to 'very severe ' after the question *'How active was your heel enthesitis on average during the last week? Please indicate your response with a vertical mark (|) through the horizontal line.'*

6.4.1.7 Magnetic resonance imaging

Disease severity and activity of PsA and axSpA can be evaluated by a variety of modalities, including magnetic resonance imaging (MRI). MRI has been frequently used to measure outcome of PsA because of its sensitivity in detecting changes in both bone and soft tissues (Yanaba et al 2015).

Effects on inflammation in the affected foot at Baseline will be assessed by MRI image analysis throughout the trial compared to pre-treatment including the following parameters (Feydy et al 2012):

[redacted]

- Bone marrow oedema in the insertion of the Achilles tendon in the upper part of the calcaneus and/or in the insertion of the plantar aponeurosis in the lower part of the calcaneus.
- [redacted]
- Periarticular inflammation.
- Resolution of signs of active inflammation.
- Bone erosions.

MRI analysis will be performed at 3 time points i.e., during pre-treatment, Week 24, and Week 52. For patients who discontinue before or at Week 24, a MRI will be performed at the time of discontinuation. MRI machines should have field strength of 1.5 Tesla. The MRI protocol and required sequences will be described in the imaging acquisition manual.

Except for the local reading of the eligibility scan for trial participation, the readings and scoring will be performed centrally. Readers will be blinded to clinical information and to the sequence of the images.

Psoriatic arthritis magnetic resonance imaging scoring system

The PsAMRIS has been developed by the Outcome Measures in Rheumatology Clinical Trial (OMERACT, Ostergaard et al 2009, McQueen et al 2009) and was based on the OMERACT rheumatoid arthritis (RA) MRI scoring system (RAMRIS) (Ostergaard et al 2003, Haavardsholm et al 2005). The PsAMRIS has shown high inter- and intraobserver reliability (Bøyesen et al 2011) and it is thought that this scoring system will be useful in measuring outcomes in the treatment of PsA. It is composed of the following six subcomponents that are assessed by a defined grading scale: synovitis, tenosynovitis, periarticular inflammation, bone oedema, bone erosions, bone proliferation.

The PsAMRIS has been originally developed for the hands (Ostergaard et al 2009) but it has recently been applied in feet MRI image analysis (Yanaba et al 2015).

Feet MRI images will be assessed for the PsAMRIS subcomponents periarticular inflammation, bone oedema and bone erosion by their respective grading scale (Ostergaard et al 2003, Ostergaard et al 2009).

Table 6-2 PsAMRIS scoring of MRIs of PsA feet

Periarticular inflammation	Score 0 or 1	0 = absent 1 = present
Bone oedema	Score 0 to 3*	0 = no oedema 1 = 1–33% of bone oedematous 2 = 34–66% 3 = 67–100%
Bone erosion	Score 0 to 10**	0 = no erosion 1 = 1-10% of bone eroded 2 = 11-20% 3 = 21-30% 4 = 31-40% 5 = 41-50%

[redacted]

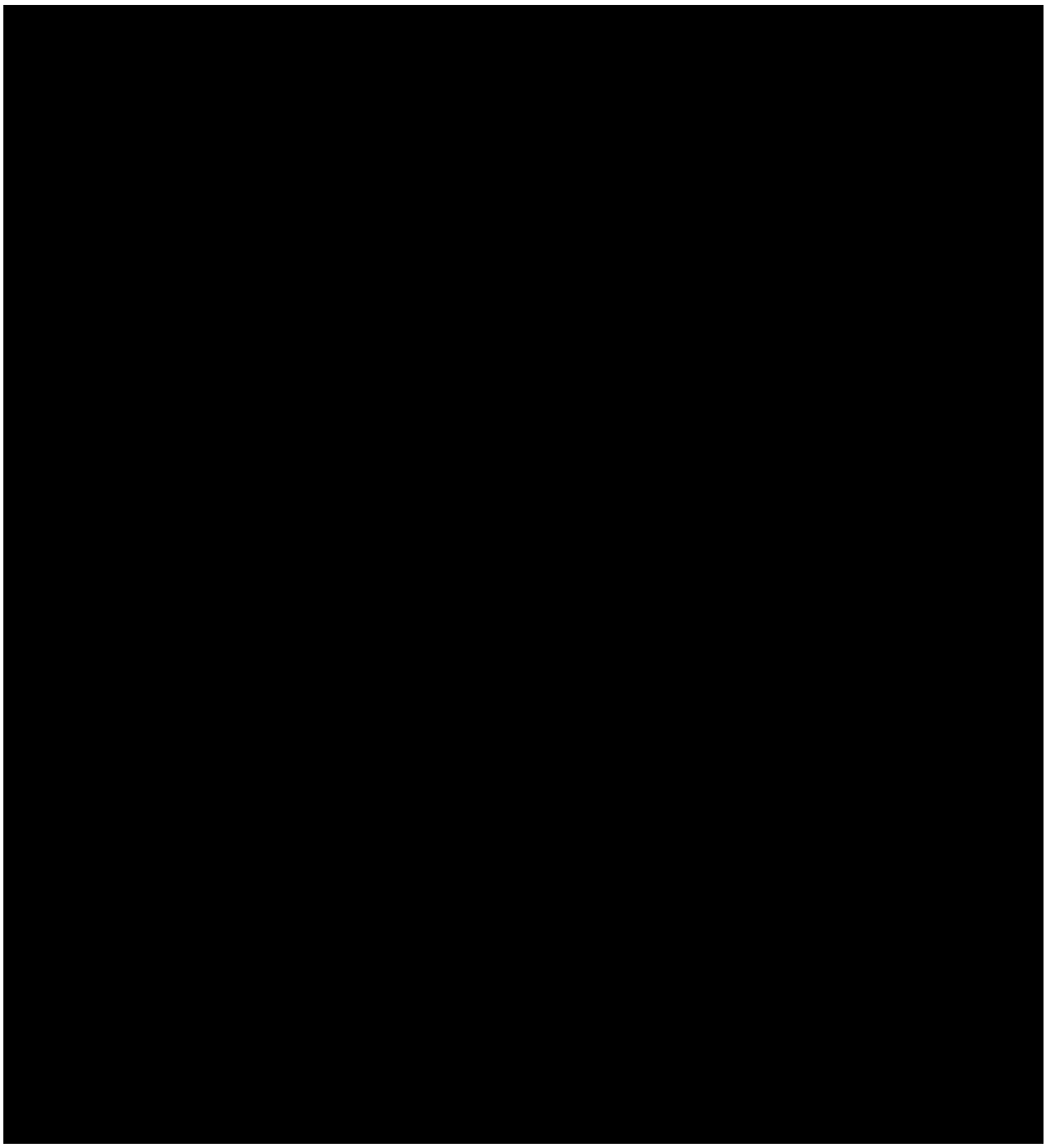
	6 = 51-60% 7 = 61-70% 8 = 71-80% 9 = 81-90% 10 = 91-100%

* The scale is 0–3 based on the proportion of bone with oedema, compared to the “assessed bone volume”, judged on all available images.

** The scale is 0–10, based on the proportion of eroded bone compared to the “assessed bone volume”, judged on all available images.

[redacted]

[redacted]



[redacted]

6.4.4 Appropriateness of efficacy assessments

The efficacy outcome measures used in this study are the standard measures used across many PsA and axSpA trials.

6.5 Safety

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

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

6.5.1 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 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 Adverse Event eCRF page.

6.5.2 Vital signs

Vital signs (including blood pressure and pulse measurements) will be assessed as indicated in Table 6-1. After the patient has been sitting for 5 minutes, with back supported and both feet placed on the floor, **systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be measured thrice** (1 to 2 minutes apart) using a validated device with an appropriately sized cuff (Mancia et al 2007); each BP measurement will be recorded in the source and mean of the three measurement will be considered for analysis. In case the cuff sizes available are

[redacted]

not large enough for the patient's arm, a sphygmomanometer with an appropriately sized cuff may be used.

If possible, assessments should be performed per patient by the same study center staff member throughout the study.

Normal blood pressure will be defined as a SBP of 90 to < 120 mmHg, and a DBP of 60 to < 80 mmHg under the measurement conditions outlined above. Notable blood pressure will be hypertension (SBP of ≥ 140 mmHg and/or DBP of ≥ 90 mmHg) or hypotension (SBP of < 90 mmHg and/or a DBP of < 60 mmHg). A blood pressure indicative of pre-hypertension (SBP of 120 to < 140 mmHg and/or DBP 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 centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured. If possible, body weight assessments should be performed by the same study site staff member using the same scale throughout the study.

6.5.4 QuantiFERON TB-Gold test

A QuantiFERON TB-Gold test must be performed at the Screening Visit and the results must to 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.

[redacted]

6.5.5.1 Hematology

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

6.5.5.2 Clinical chemistry

Serum chemistries will include glucose, urea, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), 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.

6.5.6 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as indicated in Table 6-1. All ECGs must be performed on the ECG machines provided for the study.

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

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

Clinically relevant abnormalities noted after the Baseline ECG should be reported as AEs on the Adverse Event eCRF page (see Section 7).

6.5.7 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. 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 Screening. All women who are not surgically sterile or post-menopausal (as defined in Section 4.2) 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.

6.5.8 Tolerability of secukinumab

Tolerability will be assessed by AEs, laboratory values and injection site reactions.

6.5.9 Additional parameters

Blood will be obtained at Screening (Visit 1) for anti-CCP antibodies and the RF assessment (see Table 6-1).

[redacted]

6.5.10 Appropriateness of safety measurements

The safety measures used in this study are reliable and relevant standard measures for a biologic in PsA and axSpA. The radiation exposure that results from the chest X-ray safety measurements at screening 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.

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

6.6 Other assessments

- Medical outcome short form (36) health survey (SF-36 v2).
- [redacted]
- Human leukocyte antigen B27 (HLA-B27).

6.6.1 Medical outcome short form (36) health survey

The SF-36 is a widely used and extensively studied instrument to measure HRQoL among healthy subjects and patients with acute and chronic conditions. It consists of 8 subscales that can be scored individually: physical functioning, role- physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health (Ware et al 1993). Two overall summary scores, the PCS and the Mental Component Summary also can be computed (Ware et al 1994). The SF-36 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual patients.

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

[redacted]

[redacted]

[redacted]

6.6.5 Human leukocyte antigen B27

A blood sample to analyze Human leukocyte antigen-B27 (HLA-B27) will be obtained from all patients at Screening.

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

6.6.6 Resource utilization

Not applicable.

6.6.7 Pharmacokinetics

Not applicable.

6.6.8 Other biomarkers

Not applicable.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study 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 adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events 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.

[redacted]

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

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

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

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

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment (Yes/No)
- 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 serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding study treatment

All adverse events 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 adverse event
- 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)

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

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the patient informed consent and should

be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification 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 adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information 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 adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - 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.

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

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic

[redacted]

bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

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

7.2.2 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 84 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 is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to *each specific component of study treatment, (if study treatment consists of several components)* complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. 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. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

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 Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

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.

[redacted]

The following two categories of abnormalities/adverse events 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 Table 14-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 14-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 14-2 in Appendix 2.

For the liver laboratory trigger:

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

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

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

For the liver events:

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

These investigations can include serology tests, imaging and pathology assessments, hepatologist'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

To date, there has been no safety signal for nephrotoxicity with secukinumab in over 12,000 patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the kidney. All subjects with laboratory tests resulting in clinically significant abnormal values (see Appendix 1 for notable laboratory values) are to be followed until the values return to normal ranges or until a valid reason, other than treatment

[redacted]

related AE, is defined. Standard renal function tests (blood urea nitrogen, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

7.5 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 DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in Adverse Event 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

7.6 Pregnancy reporting

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

To ensure patient safety, each pregnancy 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.

[redacted]

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 eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization, Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF 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 eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/subjects will be disclosed.

8.2 Data collection

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

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

8.3 Database management and quality control

Novartis staff [or CRO working on behalf of Novartis] review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an

[redacted]

electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff 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).

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

MRI image analysis will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

All patient questionnaires will be completed using an electronic device, processed centrally and sent electronically to Novartis (or a designated CRO).

Randomization codes and data about study drug dispensed to the patient and all dosage changes will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The 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.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

The analysis will be conducted on all patient data after data base lock for the respective trial periods. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

[redacted]

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, miss-randomized patients (miss-randomized in IRT) will be excluded from the randomized set.

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. For patients randomized erroneously into the wrong stratum, the actual stratum will be used for analyses.

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

9.2 Patient demographics and other baseline characteristics

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

9.3 Treatments

Study treatment

The analysis of study treatment data will be based on the safety set.

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

Prior and concomitant treatment

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

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

Treatments will be presented in alphabetical order, by Anatomical Therapeutic Classification codes and grouped by anatomical main group. Tables will also show the overall number and percentage of patients receiving at least one treatment of a particular Anatomical Therapeutic Classification.

[redacted]

9.4 Analysis of the primary variable

9.4.1 Variable

The primary endpoint variable is the percentage of patients with resolution of Achilles tendon enthesitis as assessed by the respective subcomponent of the LEI at 24 weeks. This resolution is referred to as 'response' below.

9.4.2 Statistical model, hypothesis, and method of analysis

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

Let pj denote the proportion of responders at Week 24 for treatment group j, j=0, 1, where

- 0 corresponds to placebo
- 1 corresponds to secukinumab

The following hypotheses will be tested:

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

In other words:

HA: The odds ratio of achieving a response at Week 24 for secukinumab vs Placebo is different from 1.

The primary analysis will be performed comparing treatments with respect to the primary efficacy variable in a logistic regression model with the factors treatment, TNFα inhibitor status and stratification factor diagnosis (PsA or axSpA). The odds ratio and its 95% confidence interval and p-value will be given.

9.4.3 Handling of missing values/censoring/discontinuations

This study aims to estimate the magnitude of treatment effects that are obtainable under the respective treatments. The disease activity is expected to decrease in the course of treatment. If a patient drops out or discontinues the trial prematurely, the last observed value of that patient seems to be a proper estimate for the effect achieved in that patient.

For the primary endpoint, a patient with a missing assessment will be considered as a responder if he/she has met the response criterion already at the time of drop-out. Otherwise he/she will be considered as a non-responder.

For the confirmatory analyses of secondary endpoints related to physician's/patient's global assessment and SF-36, missing values will be replaced by the last observed value in that patient (Last Observation Carry Forward). In case of a substantial number of missing values, alternative approaches (RMREM, MI) may be additionally calculated as sensitivity analyses.

9.4.4 Sensitivity analyses

A possible effect modification of patient characteristics will be explored by subgroup analyses for sex, age class, TNFα inhibitor status and disease severity at Baseline. The primary model

[redacted]

may also be recalculated with these factors included as well as with respective terms for a subgroup*treatment interaction. In case of a substantial number of missing values, alternative approaches to handle missing values (RMREM, MI) may be additionally calculated as sensitivity analyses.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

9.5.1.1 Heel pain

The mean change from Baseline of heel pain at 24 weeks, measured on a 10-point NRS will be analyzed using an Analysis of covariance (ANCOVA)-model with factors treatment, country and diagnosis (PsA or axSpA) and with covariate baseline heel pain. The adjusted (LS-) mean difference will be calculated as a point estimate together with its corresponding 95% confidence interval and p-value.

9.5.1.2 Percentage of patients with an improvement of bone marrow oedema

The percentage of patients with an improvement of bone marrow oedema will be analyzed using a logistic regression model analogous to the one described above for the primary endpoint.

9.5.1.3 Physician's/patient's global assessment

Physician's/patient's global assessment, measured on a VAS scale will be analyzed using an ANCOVA model analogous to that used for heel pain.

9.5.1.4 SF-36

The score of the SF-36 will be analyzed using an ANCOVA model analogous to that used for heel pain.

9.5.1.5 Time courses of primary and secondary endpoints

The time courses of primary and secondary endpoints (percentage of patients with resolution of Achilles tendon enthesitis, heel pain NRS and Physician's / patient's global assessment, VAS) will be summarized descriptively for all visits from Baseline until Week 52. Summary statistics will include relative and absolute frequencies for the binary variable 'resolution of enthesitis', and the number of patients (N), minimum, mean, median and maximum for the NRS/VAS variables. Additionally, these time courses will be displayed graphically.

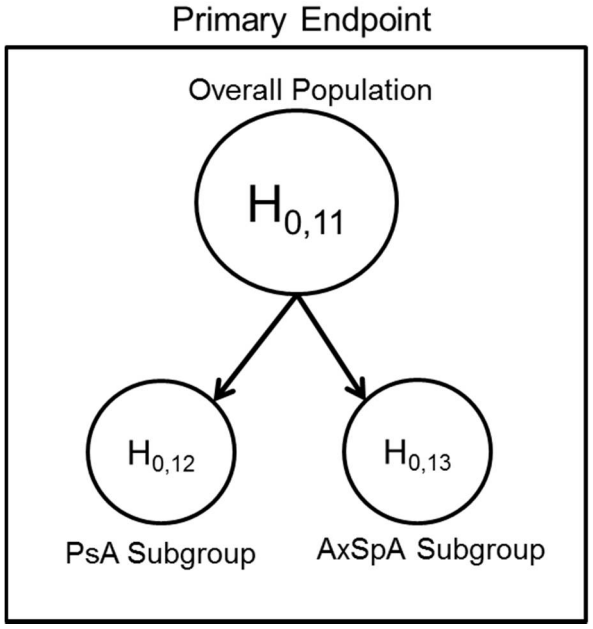
9.5.1.6 Preplanned subgroup analyses

The primary endpoint (percentage of patients with resolution of Achilles tendon enthesitis) will additionally be analyzed separately for the subgroups of patients with PsA or axSpA as well as TNFα inhibitor status, using the same model as for the respective pooled, overall population tests. Those subgroup analyses within PsA or axSpA patients are included in the confirmatory testing strategy (see below). Additional subgroup analyses may be conducted post-hoc as required as exploratory evaluations only.

[redacted]

9.5.1.7 Confirmatory testing strategy

The primary endpoint will be confirmatorily tested in the pooled, overall population as well as in the two complementary subgroups of patients with PsA or axSpA.



If the null hypotheses has been rejected for the overall population, it will then be tested for both subgroups simultaneously, both at the significance level 0.05. If the null-hypothesis is false for the overall population, it can logically not be true for both complementary subgroups. Therefore both subgroups can be tested at the same significance level $\alpha = 0.05$ without any further adjustments for multiplicity of subgroups. This procedure provides strong control of the familywise type-I-error at $\alpha = 0.05$.

All secondary endpoints will be tested exploratively outside the confirmatory framework.

9.5.2 Safety variables

9.5.2.1 Adverse events

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

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

[redacted]

These summaries may be presented separately by study periods, i.e., Weeks 1-24 and after Week 24.

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

9.5.2.2 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 assessments.

For each parameter, the maximum change from Baseline within each study period will be analyzed analogously.

9.5.2.3 Vital signs

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

[redacted]

9.7 Interim analyses

Once all data until/including Week 24 (containing the primary and secondary endpoints) are complete and clean, the database for that study period may be locked and analyzed. The results may be published or made available to personnel involved in data collection of this study prior to database lock of the complete study period until Week 52.

9.8 Sample size calculation

The primary endpoint of this trial is the percentage of patients with resolution of Achilles tendon enthesitis assessed by application of firm pressure with the pulp of the thumb by the physician at Week 24. The sample size calculation is based on the same enthesitis assessment we performed within the FUTURE 2 PsA trial (CAIN457F2312) in the form of the LEI which is composed of three different enthesial sites (Lateral epicondyle, left and right; Medial femoral condyle, left and right; Achilles tendon insertion, left and right). Within this trial, the resolution of enthesitis amongst those patients with these symptoms at Baseline has been assessed for Week 24:

[redacted]

Week 24, the end of the placebo-controlled phase:

- Secukinumab (300 mg): 48.2% of patients.
- Secukinumab (150 mg): 42.2% of patients.
- Placebo: 21.5% of patients.

In addition to these clinical data we can make the following assumptions:

- There is no difference in response to secukinumab between the different enthesial sites assessed as part of the LEI in the FUTURE 2 trial. Therefore we do not expect a different response when we only assess the Achilles tendon insertion.
- There is no difference in secukinumab response rates regarding resolution of enthesitis between PsA and axPsA patients. Therefore we pool the analysis for both diseases.

A total of 89 patients per arm are required to achieve 90% power to detect a difference on a two-sided, 5% significance level, if the true response rates are 45% under secukinumab and 21% under placebo. To account for some drop-outs and other protocol violations, 100 patients per arm = 200 patients total should be recruited into this trial.

For the comparison within the 2 subgroups of PsA and axSpA patients, which will consist of approximately 50% of the total study population each, the trial will have about 58% power with regard to the primary endpoint.

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/subjects 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 informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by

[redacted]

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

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/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances

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

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

11.1 Protocol amendments

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

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

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

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15 Appendix 3: The classification criteria for psoriatic arthritis (CASPAR)

To meet the Classification of Psoriatic Arthritis (CASPAR) criteria for diagnosis of psoriatic arthritis according to (Taylor et al 2006), a patient must have inflammatory articular disease (joint, spine or entheseal) and at least 3 points (out of 6) from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis:
   - Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.* (**2 points**)
   - 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. (**1 points, only if current psoriasis is NOT present**)
   - A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report. (**1 points, only if current psoriasis or personal history of psoriasis is NOT present**)
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 patient. If the total score ≥ 3, the patient meets CASPAR criteria for PsA diagnosis).

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

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

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

Sacroiliitis on imaging* plus ≥ 1 SpA feature	OR	HLA-B27 plus ≥ 2 other SpA features
*Sacroiliitis on imaging: Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA Definite radiographic sacroiliitis according to the modified NY criteria	SpA features: Inflammatory back pain Arthritis Enthesitis (heel) Uveitis Dactylitis Psoriasis Crohn's/colitis Good response to NSAIDs Family history for SpA HLA-B27 Elevated CRP	

17 Appendix 5: Modified New York criteria

Clinical criteria:

- Low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved by rest.
- Limitation of motion of the lumbar spine in the sagittal and frontal planes.
- Limitation of chest expansion relative to normal values correlated for age and sex.

Radiological criterion:

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

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

[redacted]

[redacted]

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

Before trial start

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

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

Before completion

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

During completion

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

After completion

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

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

Addressing problems and concerns

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

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

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

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

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

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

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

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

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

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

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

The patient asks the meaning of a question/item

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

General information about all questionnaire(s):

All questionnaires have to be completed by the patients in their local languages using an electronic device. The questionnaires should be completed by the patients in a quiet area free from disturbance, and before any visit assessments. Patients should receive no help from family members; if questions cannot be answered alone (due to problems with reading or understanding), then the doctor or nurse should read the questions and record the patient's responses without influencing their answers. The information provided is strictly confidential and will be treated as such. If a patient has missed a question or given more than one response

[redacted]

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.

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