NOVARTIS

US Clinical Development and Medical Affairs

AIN457/Secukinumab

Clinical Trial Protocol CAIN457FUS06 / NCT03350815

A randomized, double-blind, parallel-group, multicenter study of secukinumab to compare 300 mg and 150 mg at Week 52 in patients with Ankylosing Spondylitis who are randomized to dose escalation after not achieving inactive disease during an initial 16 weeks of open-label treatment with secukinumab 150 mg (ASLeap)

Document type:	Amended Protocol Version
EUDRACT number:	Not Applicable
Version number:	v04 (Track Changes)
Clinical trial phase:	IV
Release date:	20-Aug-2020

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse event
ALT/SGPT	Alanine aminotransferase/serum glutamic pyruvic transaminase
AS	Ankylosing Spondylitis
ASAS	Ankylosing SpondyloArthritis International Society
ASAS-HI	ASAS Health Index
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
AST/SGOT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase
BASDAI	Bath Ankylosing Spondylitis Disease Activity index
[redacted]	[redacted]
BMI	Body mass index
BSL	Baseline
COPD	Chronic obstructive pulmonary disorder
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract research organization
CRP	C-reactive protein
CSR	Clinical study report
CTC	Common Toxicity Criteria
DMARD	Disease Modifying Anti-rheumatic Drug
DS&E	Drug Safety & Epidemiology
DSM	Drug supply management
eCRF	Electronic Case Report/Record Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA/EMEA	European Medicines (Evaluation) Agency
FACIT-Fatigue©	Functional Assessment of Chronic Illness Therapy – Fatigue
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
[redacted]	[redacted]
IB	Investigator's brochure
IBD	Inflammatory Bowel Disease
ICF	Informed consent form
IEC	Independent Ethics Committee
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFU	Instructions for use
IL	Interleukin
IRB	Institutional Review Board
IRT	Interactive Response Technology

IUD	Intra Uterine Device
IUS	Intra Uterine System
i.v.	intravenous(ly)
LFT	Liver function test
LLN	Lower limit of normal
[redacted]	[redacted]
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging/image
mmHg	Millimeter mercury
MTX	Methotrexate
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
PBO	Placebo
PFS	Prefilled syringe
PPD	Purified protein derivative
PRN	Pro re nata (as required)
PRO	Patient Reported Outcome
PsA	Psoriatic arthritis
QoL	Quality of Life
RA	Rheumatoid arthritis
RBC	Red blood cell
SAE	Serious adverse event
s.c.	Subcutaneous(ly)
SCR	Screening
SD	Standard deviation
SE	Sleep efficiency
SI	Sacroiliac
SpA	Spondyloarthritis
SUSAR	Suspected Unexpected Serious Adverse Reactions
SV1	Screening Visit 1
SV2	Screening Visit 2
ULN	Upper limit of normal
VAS	Visual analog scale
[redacted]	[redacted]
WBC	White blood cell
WHO	World Health Organization

Glossary of Terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
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
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
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)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Premature subject withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Amendment 04

Amendment rationale

This protocol has been modified to add telemedicine/telephone study visits with direct to patient shipment of study drug as options available to participants unable to travel to the clinic for a study visit as the result of the COVID19 pandemic. Given the study design, which already allows flexible (home nursing) visits, the addition of telemedicine/telephone study visits with direct to patient shipment of study drug is believed to pose minimal risk to patient safety and data integrity.

The definition of withdrawal of consent was also updated.

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.

IRBs/IECs

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

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

Summary of previous amendments

Amendment 3 (15-Oct-2018)

The protocol has been modified to require a patient's documented radiologic evidence to be read by a central reader at Screening Visit 2, correct the total minimum number of weeks during the screening period in Figure 3-1, clarify the women of childbearing potential exclusion, amend the wash-out period length for TNFα inhibitors in Table 5-1 and exclusion 10, clarify that a chest x-ray is required within 3 months prior to screening in section 6.6.2, to bullet the list of parameters used for the ASDAS calculation in section 6.5.1, add a section reference to Table 6-1 Assessment schedule and make grammatical corrections.

Amendment 2 (07-Feb-2018)

The protocol has been modified to correct the definition of an Inadequate Responder, revise the screening period assessments related to the delivery of the wearable sensor, reconcile visit assessment inconsistencies, remove duplicate text and revise concomitant medication requirements. Additionally, copy/paste errors have been removed and protocol clarifications have been made at certain points.

Amendment 1 (14-Dec-2017)

The protocol has been modified to change from the use of visual analog scales (VAS) to numeric rating scales (NRS) for the following patient reported outcomes measures: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), [redacted]

[redacted] Additionally, reconciliation of minor inconsistences and protocol clarifications have been made at certain points.

Protocol Summary

Protocol number	CAIN457FUS06
Full Title	A randomized, double-blind, parallel-group, multicenter study of secukinumab to compare 300 mg and 150 mg at Week 52 in patients with Ankylosing Spondylitis who are randomized to dose escalation after not achieving inactive disease during an initial 16 weeks of open-label treatment with secukinumab 150 mg (ASLeap)
Brief title	Study estimating the clinical difference between 300 mg and 150 mg of secukinumab following dose escalation to 300 mg in patients with ankylosing spondylitis
Sponsor and Clinical Phase	Novartis Phase IV
Investigation type	Interventional
Study type	Randomized, double-blind, parallel-group, multicenter
Purpose and rationale	The purpose of this study is to estimate the difference in clinical response between 300 mg and 150 mg of secukinumab at Week 52, which follows randomization to dose escalation at Week 16 for patients with Ankylosing Spondylitis who inadequately respond to open-label secukinumab 150 mg. This study will also investigate the association between treatment and sleep disturbances, as well as daytime activity patterns. In January 2020, the FDA approved 300 mg as a dosage to be considered if a patient continues to have active ankylosing spondylitis. There continues to be a need to understand the impact of 300 mg in the treatment of AS in response to not achieving a pre-established target clinical response on 150 mg, such as disease remission, to evaluate the impact of increased dose on subsequent clinical outcomes, for which this study aims to assess.
Primary Objective(s)	To estimate the difference between secukinumab 300 mg and secukinumab 150 mg treatment groups at Week 52 based on the proportion of subjects achieving ASDAS inactive disease (< 1.3) status who did not meet ASDAS inactive disease criteria at Week 12 and Week 16.
Secondary Objectives	• To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving a ASDAS clinically important improvement from their Week 16 ASDAS score (reduction in ASDAS ≥ 1.1 from Week 16) • To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the change from Week 16 in the total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) • To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving BASDAI50 response

	• To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving an Assessment of Spondyloarthritis International Society criteria 20 response (ASAS20) • To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving ASAS40 response • To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving ASAS partial remission (a value not above 2 units in each of the four main domains on a scale of 10) • To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on change from Week 16 in the total score of ASAS Health Index (ASAS-HI) • To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on change from Week 16 in the total score of FACIT-Fatigue • The overall safety and tolerability of secukinumab
Study design	This study design includes an initial 16 week open-label period (Treatment Period 1) followed by a randomized, double-blind, parallel-group period (Treatment Period 2). During the initial 16 weeks of the trial, all patients will receive open-label 150 mg secukinumab. At Week 16, based on whether they have met the definition of ASDAS inactive disease, patients will be placed into one of the following three groups for the remaining 36 weeks of the trial. • Responders: Patients that achieve ASDAS inactive disease (total score < 1.3) at **both** Week 12 and Week 16 and who do achieve a decrease (improvement) from baseline in total ASDAS score at both Week 12 and Week 16. Patients will enter Treatment Period 2 and continue receiving secukinumab 150 mg through Week 48. • Inadequate Responders: Patients who have active disease, defined as an ASDAS total score of ≥ 1.3 at either Week 12 or Week 16, and do achieve a decrease (improvement) from baseline in total ASDAS score at both Week 12 and Week 16. Patients will enter Treatment Period 2 and be randomized (1:1, double-blinded) to secukinumab 300 mg or secukinumab 150 mg through Week 48. • Non-responders: Patients who exhibit no change or an increase (worsening) from baseline in total ASDAS score at either Week 12 or Week 16. Patients will terminate the study at Week 16.
Population	The study population will consist of male and female patients, ≥ 18 years of age with a clinical diagnosis of moderate to severe AS fulfilling the Modified New York criteria for AS and with moderate to severe disease

	despite previous or current NSAIDs / non-biologic DMARDs and/or anti-TNFα therapy. Patients must have a history of active AS, as measured by the following three assessments: • Total BASDAI of ≥ 4 on a numeric rating scale (NRS) of 0-10 at baseline • Spinal pain as measured by BASDAI question #2 of ≥ 4 on a NRS of 0-10 at baseline • Total back pain of ≥ 4 on a NRS of 0-10 at baseline The study aims to enroll approximately 270 patients at approximately 82 centers in the United States. Since a 25% screen failure rate is expected, approximately 360 patients will be screened.
Key Inclusion criteria	Patients/subjects 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 give a 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. Diagnosis of moderate to severe AS with prior documented radiologic evidence (x-ray or radiologist's report) fulfilling the Modified New York criteria for AS [redacted] 4. Active AS assessed by total BASDAI of ≥ 4 (NRS of 0-10) at baseline 5. Spinal pain as measured by BASDAI question #2 of ≥ 4 (NRS of 0-10) at baseline 6. Total back pain of ≥ 4 (NRS of 0-10) at baseline 7. Patients should have been on NSAIDs at the maximum tolerated dose for at least 4 weeks prior to their Baseline Visit, with an inadequate response or for less than 4 weeks if withdrawn for intolerance, toxicity or contraindications 8. Patients who are regularly taking NSAIDs (including COX-1 or COX-2 inhibitors) as part of their AS therapy are required to be on a stable dose for at least 2 weeks before their Baseline Visit 9. Patients who have been on a TNFα inhibitor (not more than one) must have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months prior to baseline or had been intolerant upon administration of that anti-TNFα agent
Key Exclusion criteria	Patients/subjects fulfilling any of the following criteria during the Screening Period or at the Baseline Visit 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/subjects. 1. Patients with total ankylosis of the spine

	2. Use of other investigational drugs within 5 half-lives of enrollment, or within 4 weeks before the Baseline Visit, whichever is longer. 3. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes. 4. Chest x-ray, CT scan, or chest magnetic resonance imaging (MRI) with evidence of ongoing infectious or malignant process, obtained within 3 months prior to screening and evaluated by a qualified physician. 5. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17, IL-12/23, or the IL-17 receptor, or any other biologic immunomodulating agent, except those targeting TNFα 6. Patients who have taken more than one anti-TNFα agent 7. Any intramuscular or intravenous corticosteroid injection within 2 weeks before baseline 8. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before baseline 9. Active ongoing inflammatory diseases other than AS that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease or uveitis 10. 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)
Study treatment	All patients will receive active secukinumab. During the first 16 weeks of the trial, all patients will receive 150 mg secukinumab. During the remaining 36 weeks of the trial, patients will receive either 150 mg or 300 mg secukinumab.
Efficacy assessments	• Ankylosing Spondylitis Disease Activity Score (ASDAS) and ASDAS response categories • Assessment of Spondyloarthritis International Society criteria (ASAS) • [redacted] • [redacted] • [redacted] • Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) • [redacted] • ASAS-Health Index (ASAS-HI) • [redacted] • FACIT- Fatigue
Key safety assessments	• AEs and SAEs including injection site reactions • ECGs • Physical examination

	• Vital signs • Laboratory assessments • Assessment of anti-secukinumab antibody development (immunogenicity)
Other assessments	• [redacted] • [redacted]
Data analysis	The analysis will be conducted on all patient data at the time the trial ends. Efficacy, safety, and other data from Treatment Period 1, randomized double-blind Treatment Period 2 for inadequate responders, and blinded Treatment Period 2 for responders will be summarized. For continuous variables, summary statistics (mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum) at each time point and for change from baseline to Week 16, and change from Week 16 to each time point by treatment group will be reported. For discrete variables, frequency counts and percentages at each time point will be reported by treatment group. The following analysis sets will be used for the statistical reporting and analyses: Enrolled Set: The Enrolled Set consists of all enrolled patients for the initial 16-week, Treatment Period 1. Responder Set: The Responder Set consists of all patients who are labeled as responders at the end of Treatment Period 1, and enter Treatment Period 2 receiving blinded secukinumab 150 mg every 4 weeks through Week 48. Randomized Set: The Randomized Set consists of all randomized patients. Safety Set: The Safety Set includes all patients who received at least one dose of study treatment during Treatment Period 2. Patients will be analyzed according to the study treatment received. Full Analysis Set: The Full Analysis Set comprises all patients to whom study treatment has been assigned by randomization. Patients inappropriately randomized (e.g., IRT was called in error for randomization of a screen failed patient) will be excluded from this analysis set. According to the intent-to-treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure. The primary efficacy variable is the ASDAS inactive disease response (yes, no). The primary analysis time point is at Week 52. The primary efficacy variable will be analyzed at each time point using a logistic regression model with treatment, TNF-alpha inhibitor status (naive, inadequate responder), and baseline body weight as explanatory variables (Stokes, Davis, and Koch, 2012). The odds ratios and 95% confidence intervals for the odds ratios will be reported, based on the fitted model.

	Post-randomization patients who discontinue prematurely for any reason will be considered non-responders from the time they discontinued. In an additional analysis, missing data for ASDAS inactive disease response will be imputed using multiple imputation. The secondary efficacy variables are the following: 1. Reduction in ASDAS ≥ 1.1 from Week 16 (yes, no) 2. Change from Week 16 in total BASDAI 3. BASDAI50 response (yes, no) 4. ASAS20 response (yes, no) 5. ASAS40 response (yes, no) 6. ASAS partial remission (yes, no) 7. Change from Week 16 in ASAS-Health Index 8. Change from Week 16 in FACIT-Fatigue Analyses of secondary efficacy variables 1 and 3-6 at each time point will be similar to the analyses of the primary efficacy variable. Secondary efficacy variables 2, 7, and 8 will be analyzed at each time point by an analysis of covariance model with treatment, Week 16 value, TNF-alpha inhibitor status (naive, inadequate responder), and baseline body weight as explanatory variables. The least squares means of the treatment groups, least squares mean difference, and 95% confidence interval for the difference will be reported, based on the fitted linear model. Missing data will be imputed using the last-observation-carried-forward method. In an additional analysis, missing data will be imputed using multiple imputation. Analyses of the primary and secondary efficacy variables will be based on the Full Analysis Set. The assessment of safety will be based mainly on the frequency of adverse events and laboratory data. For safety analyses, the Enrolled Set will be used for Treatment Period 1, and the Safety Set will be used for Treatment Period 2. The sample size was calculated based on the primary efficacy variable (i.e., ASDAS inactive disease response) at Week 52 for the Full Analysis Set. The expected ASDAS inactive disease response rates for secukinumab 300 mg and 150 mg treatment groups at Week 52 are 20% and 10%, respectively (corresponding to an odds ratio of 2.25), partly based on results from AIN457F2310 (MEASURE 2) study. With approximately 97 patients in each treatment group (total of 194 randomized patients), one will be able to estimate the difference between ASDAS inactive disease response rates of the two treatment groups at Week 52 with a “margin of error” (half-width of confidence interval) of 10% (corresponding to a standard error of 5%) for a two-sided 95% confidence interval (Julious and Patterson, 2004; nQuery Advisor 7.0). It is expected that the study will need to enroll approximately 270 patients for Treatment Period 1, to randomize approximately 194 patients who do not achieve ASDAS inactive disease status at Week 16 (inadequate responders). This assumes that 10% of the 270 enrolled patients will discontinue during Treatment Period 1; among the remaining enrolled

	patients, it is assumed that approximately 10% will be responders, 80% will be inadequate responders, and 10% will be non-responders.
Key words	Ankylosing spondylitis, ASDAS inactive disease, sacroiliitis, secukinumab

1 Introduction

1.1 Background

Ankylosing spondylitis (AS) is a chronic inflammatory disease which belongs to a group of conditions known as spondyloarthritides. AS is mainly characterized by involvement of the axial skeleton and sacroiliac joints, but it also affects peripheral joints, entheses and extraarticular organs. A significant proportion of patients may present with associated extraarticular manifestations such as uveitis, psoriasis, inflammatory bowel disease (IBD), cardiovascular and pulmonary abnormalities. Generalized osteoporosis, as well as regional osteopenia are common in AS patients and predispose them to non-traumatic fractures in spite of young age and gender (male). The presence of the HLA-B27 human leukocyte antigen is strongly associated with AS: 90–95% of patients with AS who have European ancestry carry this marker. AS affects up to 1.1% of the population, is associated with significant morbidity and disability, and thus constitutes a major socioeconomic burden.

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

Patients with AS report chronic and extensive sleep disturbance due to pain and stiffness during the night (Leverment 2017). Often patients get out of bed and walk around during the night to reduce pain and stiffness, which can lead to daytime fatigue (Rudwaleit 2006). In AS patients poor quality sleep is strongly correlated with increased pain, lower quality of life, higher depressed mood, higher disease activity and reduced physical function (Batzman 2013). Treatment with anti-TNF golimumab has been shown to significantly reduce sleep disturbances in AS patients over 14 weeks as assessed by questionnaire (Deodhar 2010). The effect of secukinumab on AS related sleep disturbance has not yet been studied. Additionally, there is a general lack of data to investigate associations between sleep disturbance and daytime fatigue levels in AS.

Although studies have been conducted with subjective measures of sleep in patient with AS, there have been limited assessments with quantitative measure of sleep disturbance, such as with polysomnography. A recent polysomnography study of 59 patients with AS demonstrated impairments in sleep architecture between patients on NSAID therapy, with improvements seen in total sleep time and sleep efficiency by patients treated with TNF inhibitors (In 2016). Another valid objective measure of sleep, and daytime activity, is actigraphy that measures activity with a wearable accelerometer, a digital sensor that can be worn on the wrist that measures the accelerations of the device in motion along reference axes. Actigraphic assessment data from an accelerometer typically involves integration of acceleration data (collected in units of $ms^{-1}s^{-1}$) with respect to time (Chen 2005), with a typical sample at a rate of 32-100 Hz (cycles per second). Acceleration data is condensed and stored in the device in

fixed 'epochs' of time. Actigraphic assessment of sleep disruption and daytime activity is less burdensome for patients than traditional daily assessments and much less intrusive than polysomnography while providing data that is not effected by recall or reporting biases. While untested in patients with AS, actigraphy has been successfully used in prospective interventional studies to assess the impact of pharmacological treatment on both sleep and daytime physical activity, in atopic dermatitis (Nemoto 2016), heart failure (Redfield 2015), and osteoarthritis (Trudeau 2015).

Secukinumab (AIN457) is a high-affinity human monoclonal anti-human antibody that neutralizes IL-17A activity. IL-17A is the key cytokine in the Th17 and innate immune pathways which is thought to be an important mediator of autoinflammation. Secukinumab is currently approved by the FDA to treat moderate to severe plaque psoriasis, active psoriatic arthritis, and active ankylosing spondylitis (Cosentyx® package insert).

Secukinumab has been previously evaluated in active AS in the MEASURE 1 and MEASURE 2 studies of 590 patients with AS (Baeten et al., 2015), demonstrating the efficacy of secukinumab 150 mg (S.C.) versus placebo on ASAS20 at Week 16 in both studies. Inconsistent results were seen with 75 mg, and 300 mg was not included as a dosage in these two pivotal Phase III studies. As such, secukinumab received initial FDA approval for only 150 mg of secukinumab every 4 weeks with or without loading in the treatment of active ankylosing spondylitis. A subsequent Phase III study (MEASURE 3) was conducted that included a 300 mg dose group, which demonstrated a significant difference from placebo on ASAS20 at Week 16, however the efficacy did not clinically differ from the 150 mg dose group at Week 16. Of note, this study involved an intravenous loading regimen of 10 mg/kg secukinumab at Week 0, 2 and 4, followed by s.c. dosing every 4 weeks of 150 mg or 300 mg. This intravenous loading regimen conferred initially higher concentrations of secukinumab such that a meaningful assessment between the 300 mg and 150 mg doses would not be attainable at the Week 16 primary analysis time point. However, at Week 52 and beyond, presumably when the pharmacokinetic influence of the intravenous load had waned, evaluation of higher hurdle efficacy measures (e.g., ASDAS-inactive disease, ASAS Partial Remission), revealed higher efficacy responses for 300 mg compared with 150 mg. Thus, AS patients may benefit from a 300mg regimen, however further study is required to explore dose-based differences with the approved s.c. loading regimen. Further, previous studies have not evaluated dose-escalation such as 150 mg to 300 mg in a patient subgroup that had not met a pre-defined response threshold to determine if greater efficacy could subsequently be achieved. The FDA has subsequently approved 300 mg as a dosage to be considered if a patient continues to have active ankylosing spondylitis in January 2020.

There continues to be a need to understand the impact of 300 mg in the treatment of AS, specifically within the context of enacting a therapeutic dosage change in patients who have not met an *a prioi* established target clinical response, such as a non-response threshold, or a high-response target, such as disease remission or a comparable analogue. As 300 mg is an available dose with an established safety profile comparable to 150 mg in both moderate to severe plaque psoriasis and active psoriatic arthritis and has demonstrated clinically meaningful differences compared to 150 mg on certain clinical measures (e.g., PASI, ACR50, ACR70), and patient subgroups (anti-TNF inadequate responders), it is appropriate to pursue the study of 300 mg in AS.

As of 25-Jun-2017, over 11,140 healthy subjects and patients have received at least one dose of secukinumab in clinical studies. Secukinumab studies have investigated various indications (Rheumatoid Arthritis (RA), AS, Psoriatic Arthritis (PsA), psoriasis, multiple sclerosis, uveitis, Crohn's disease, dry eye syndrome, polymyalgia rheumatica, diabetes mellitus) at doses ranging from single and multiple doses of 0.1 mg/kg to 30 mg/kg i.v. and 25 mg to 300 mg s.c. As of Jan -2016, secukinumab has been approved for the treatment of AS in the European Union, the US and multiple other countries. Full safety results from completed studies for AS, PsA and psoriasis show that secukinumab generally is safe and well tolerated. Please refer to the latest Investigator's Brochure (IB) for a more detailed review of the risk:benefit profile of secukinumab which supports the clinical development for the treatment of AS patients with secukinumab.

1.2 Purpose

The purpose of this study is to estimate the difference in clinical response between 300 mg and 150 mg of secukinumab at Week 52, which follows randomization to dose escalation at Week 16 for patients with Ankylosing Spondylitis who inadequately respond to open-label secukinumab 150 mg. This study will also investigate the association between treatment and sleep disturbances, as well as daytime activity patterns.

2 Study objective and endpoints

2.1 Objectives and related endpoints

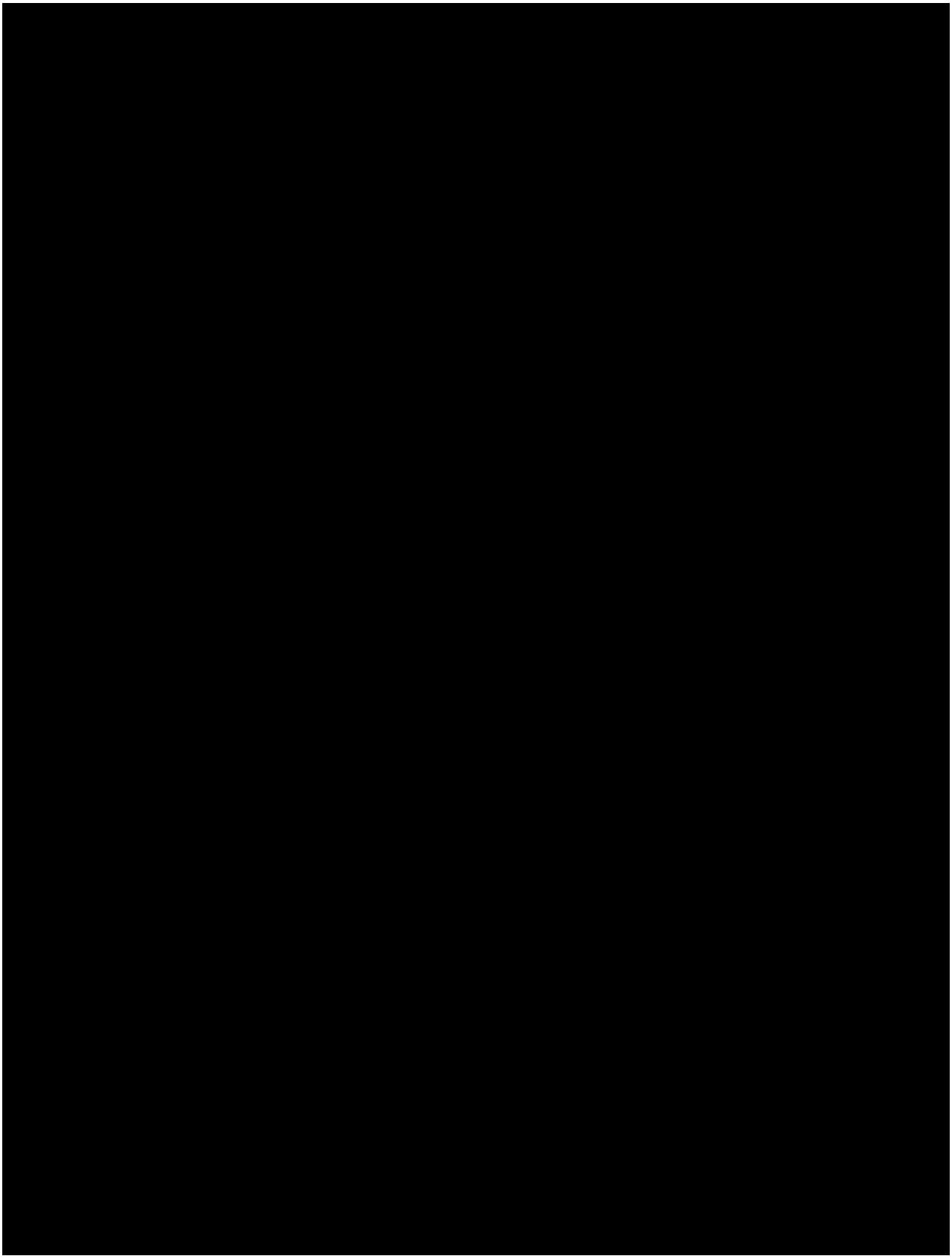
Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
1. To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving ASDAS inactive disease (< 1.3) status who did not meet ASDAS inactive disease criteria at Week 12 and Week 16.	1. The primary efficacy variable is the ASDAS inactive disease response (yes, no). The primary analysis time point is at Week 52.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
1. To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving a ASDAS clinically important improvement from their Week 16 ASDAS score (reduction in ASDAS ≥ 1.1 from Week 16) 2. To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the change from Week 16 in the	1. Reduction in ASDAS ≥ 1.1 from Week 16 (yes, no) 2. Change from Week 16 in total BASDAI 3. BASDAI50 response (yes, no) 4. ASAS20 response (yes, no) 5. ASAS40 response (yes, no) 6. ASAS partial remission (yes, no) 7. Change from Week 16 in ASAS-Health Index

Objective(s)	Endpoint(s)
total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 3. To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving BASDAI50 response	8. Change from Week 16 in FACIT-Fatigue

Objective(s)	Endpoint(s)
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
4. To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving an Assessment of Spondyloarthritis International Society criteria 20 response (ASAS20)	
5. To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving ASAS40 response	
6. To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving ASAS partial remission (a value not above 2 units in each of the four main domains on a scale of 10)	
7. To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on change from Week 16 in the total score of ASAS Health Index (ASAS-HI)	
8. To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on change from Week 16 in the total score of FACIT-Fatigue	
9. The overall safety and tolerability of secukinumab	

[redacted]



3 Investigational Plan

3.1 Study design

This study will use a randomized, double-blind, parallel-group design, multicenter design.

There are 3 study periods:

1. **Screening:** A screening period will take place over two separate visits, with the first visit used to assess eligibility and to washout prohibited medications (up to 11 weeks). The second screening visit, which will occur at a minimum of 2 weeks prior to the baseline visit for all patients. [redacted] **Note: Patients that do not require a washout, and who satisfy all inclusion and none of the exclusion criteria at the first screening visit can initiate the second screening visit one week after their first screening visit.**
2. **Treatment Period 1:** Patients who meet all of the inclusion criteria and none of the exclusion criteria will have a Baseline Visit performed to start Treatment Period 1. During this 16-week period, all patients will receive open-label secukinumab 150 mg [1 x 1.0mL s.c.] at baseline, Weeks 1, 2, 3, 4, 8, and 12.

   At Week 16, patients will be placed into one of the following groups:

   a. Responders: Patients achieving ASDAS inactive disease (total score < 1.3) at **both** Week 12 and Week 16 and who do achieve a decrease (improvement) from baseline in total ASDAS score at both Week 12 and Week 16.
   b. Inadequate responders: Patients who have active disease, defined as an ASDAS total score of ≥1.3 at either Week 12 or Week 16, and who do achieve a decrease (improvement) from baseline in total ASDAS score at both Week 12 and Week 16.
   c. Non-responders: Patients who exhibit no change or an increase (worsening) from baseline in total ASDAS score at **either** Week 12 **or** Week 16

Note: To minimize patient burden, at the Week 16 visit, the hs-CRP measurement that is part of the ASDAS calculation will be imputed from the Week 12 hs-CRP results to allow for assignment into the groups above. Historically, hs-CRP levels have varied little between Week 12 and Week 16 or in previous studies of secukinumab in active AS.

3. **Treatment Period 2:** Upon completion of the Week 16 visit,

   a. **Responders** will enter Treatment Period 2 and continue to receive secukinumab 150 mg every 4 weeks through Week 48 as well as one matched placebo dose (s.c. injection) to maintain the integrity of the blind for the randomized Inadequate Responder group.

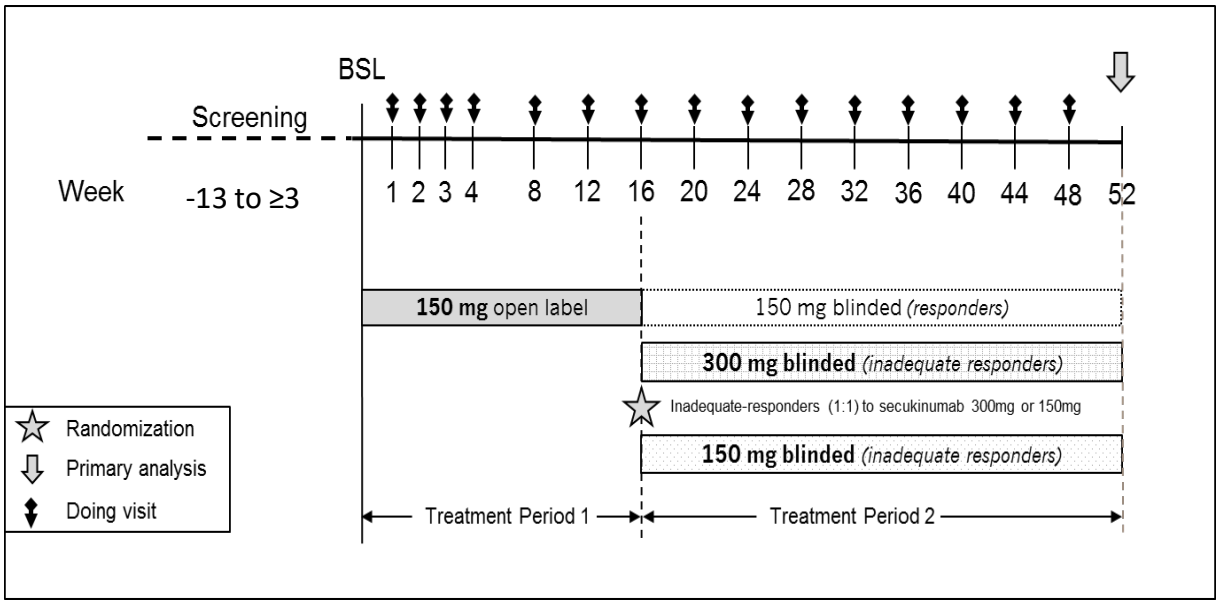
b. **Inadequate responders** will enter Treatment Period 2 and will be randomized (1:1, double-blinded) to secukinumab 300 mg or secukinumab 150 mg very 4 weeks through Week 48. Subjects will know that they are on secukinumab, but will be blinded to dose, as they will not know whether they are receiving 150 mg or 300 mg.

c. **Nonresponders** will be discontinued from the study at Week 16.

The only condition that will be placed on enrollment targets is that no less than 60% of patients (162 patients) are TNFα inhibitor naive (or, no more than 40% of patients are TNF-IR). In theory the percentage of TNFα inhibitor naive patients could reach 100%, although that is not anticipated.

Patients may discontinue the study at any time. If rescue treatment with prohibited medications [redacted] occurs, patients will be discontinued from the study and should return for an End of Study Visit (see Table 6-1). The End of Study Visit should be scheduled approximately four weeks after the last study treatment, and should be performed before any new treatment is initiated. After the End of Study Visit, any SAEs that occur in the following 30 days must be reported.

Figure 3-1 Study design



3.2 Rationale for study design

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

The two visit Screening Period is designed to allow for both (1) washout of prohibited medications, and [redacted]

[redacted]

The randomized, blinded, parallel-group design used in this study is based on the primary focus of this study, which is to estimate the difference in clinical response between either remaining on 150 mg or escalating to 300 mg of secukinumab after not achieving a measured state of inactive disease at the Week 12 and Week 16 time points. The responder status at Week 12 and Week 16, as well as the primary objective at Week 52 is determined with the validated ASDAS clinical scoring measure of disease activity status which will establish patients who score within the "inactive disease" classification of this measure (a total score of < 1.3). Week 52 has been selected as the primary analysis time point to allow sufficient time (36 weeks) for a clinical response to be observed following dose escalation to 300 mg at Week 16 vs those patients who remain on 150 mg for the entire 52-week period.

Following the Week 16 visit, randomized inadequate responder patients and investigators will be blind to the dose of secukinumab through the use of a matched placebo injection (identical in appearance) in the 150 mg s.c. group. The blinding of the secukinumab treatments (150 mg or 300 mg) will allow for an evaluation of a potential dose-response of the 150 mg and 300 mg secukinumab doses on both efficacy and safety outcomes.

Responder patients, those who achieve ASDAS inactive disease at Week 12 and Week 16, will continue on secukinumab 150 mg to evaluate the longer-term treatment response up to Week 52. To support the integrity of the blind for the randomized inadequate responder group, the responder patients will also be dose blinded between Week 16 and Week 48 by receiving a single matching placebo injection to their secukinumab 150 mg injection. Thus, all responder and inadequate responder patients will be blinded to dose and will receive two matched injections every 4 weeks. While the responder group is not the primary focus of this study, this subgroup will provide meaningful exploratory analyses of the clinical characteristics and duration of response in patients who achieve a high-level efficacious response to secukinumab at Week 16.

The population of non-responders, expected to be low in number, will be discontinued from the study at Week 16 as these patients would be considered a primary failure of therapy. Non-responders, by the criteria of no measured improvement, or a worsening of disease activity after 16 weeks of treatment are not expected to improve with a dose escalation, and thus are to terminate the study to seek alternative treatments options that may benefit their disease.

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

The secukinumab dosing regimens in this study are based upon the currently approved dose for active ankylosing spondylitis, which is 150 mg s.c. every 4 weeks (without or with a loading regimen of 150 mg at Weeks 0, 1, 2, 3, and 4.

The rationale for the use of 300 mg of secukinumab in this study of patients with ankylosing spondylitis is motivated by the fact that 300 mg is an approved dose to treat patients with moderate-to-severe plaque psoriasis and active psoriatic arthritis. In psoriatic arthritis, it is labeled as an escalation dose for patients who remain with active disease while on a 150 mg dosing regimen. In both the psoriasis and psoriatic arthritis clinical studies, several measures demonstrated higher responses with 300 mg versus 150 mg, including the clearance of psoriatic plaques, as well as in patients who were previous inadequate responders to anti-TNFα therapies. Further, 300 mg treatment groups demonstrated a comparable safety profile to 150 mg every 4 weeks. (Langley 2014, Mease 2015).

This study will evaluate whether a higher dose of secukinumab will have an effect on subjects with AS, specifically signs and symptoms of AS and the achievement of state of inactive disease based on the ASDAS measure. The duration of treatment of initial open-label 150 mg for 16 weeks is based on Week 16 being the primary analysis time point for the previous Phase 3 secukinumab studies in AS. While statistical separation on the ASAS20 measure occurs as early as Week 1, greater responses are seen out to Week 16 and beyond (Baeten et al., 2015). In addition, patients will receive the loading regime of weekly dose of secukinumab 150 mg at Baseline, and Week 1, 2, 3, and 4, to be consistent with previous Phase 3 studies. Patients will be assessed at each of these weekly time points at the clinical site to evaluate the onset of clinical response and ensure patients are trained and comfortable administering the pre-filled syringe.

The evaluation of clinical effect over the long-term extension of studies, reveal a steady incline in response on several measures, particularly for BASDAI and ASAS40, over the Week 16 to Week 52 to Week 104 timeframes (Marzo-Ortega 2017). Therefore, the 36-week duration of Treatment Period 2 will provide a sufficient period of time to observe any treatment differences between the 300 mg and 150 mg groups.

3.4 Rationale for choice of comparator

This study does not include a placebo arm. Efficacy in terms of signs and symptoms is well established for secukinumab 150 mg for patients with active AS. Moreover, a placebo cohort would not be deemed ethically justifiable for this 1-year study, considering AS is known to be a chronic progressive disease with structural damage.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

Secukinumab has shown efficacy in several inflammatory diseases and approved by the FDA and EMA for the treatment of adults with active AS, active PsA, and plaque psoriasis. Significant differences from placebo, etanercept and ustekinumab have been demonstrated in the treatment of psoriasis (Langley 2014; Thaçi 2015), as well as significant difference from placebo in the treatment of joint pain, swelling, health-related quality of live, and radiographic progression in PsA (Mease 2015; McInnes 2015; van der Heijde, 2016) and AS (Baeten et al 2015; Braun 2016).

The large safety dataset of secukinumab across indications involving over 9,600 subjects did not show unexpected safety issues relative to the known mode of action. Secukinumab was generally safe and well-tolerated. The most frequently reported adverse events (AEs) are non-serious mild to moderate infections, mainly upper respiratory tract infections with secukinumab relative to placebo. In addition, there was an increase in localized mucosal or cutaneous candidiasis with secukinumab compared with placebo, but the cases were generally mild or moderate in severity, non-serious, and responsive to standard treatment and did not require discontinuation of secukinumab. There was also a small increase in neutropenia cases with secukinumab compared with placebo. Most cases were mild to moderate, transient and reversible and without a temporal relationship to infections. Common Toxicity Criteria (CTC) AE grade 3 neutropenia (< 1.0-0.5 x 109/L) was uncommonly observed with secukinumab. Hypersensitivity reactions include urticaria and rare events of anaphylactic reaction to secukinumab have also been observed in clinical studies.

Taking into account the individual risks as outlined above, the expected risk profile of secukinumab from a mechanism of action perspective is anticipated to be similar or improved compared to the approved inflammatory cytokine-targeting therapies. 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 IB. From the standpoint of the overall risk-benefit assessment, current trial with secukinumab is justified.

4 Population

The study population will consist of male and female patients, ≥ 18 years of age with a clinical diagnosis of moderate to severe AS fulfilling the Modified New York criteria for AS [redacted] and with moderate to severe disease despite previous or current NSAIDs / non-biologic DMARDs and/or anti-TNFα therapy.

Patients must have a history of active AS, as measured by the following three assessments:

- Total BASDAI of ≥ 4 on a NRS of 0-10 at baseline
- Spinal pain as measured by BASDAI question #2 of ≥ 4 on a NRS of 0-10 at baseline
- Total back pain ≥ 4 on a NRS of 0-10 at baseline

The study aims to enroll approximately 270 patients at approximately 82 centers in the United States. Since a 25% screen failure rate is expected, approximately 360 patients will be screened.

Patients who drop out after they have been randomized will not be replaced.

4.1 Inclusion Criteria

Patients/subjects 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 give a 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. Diagnosis of moderate to severe AS with prior documented radiologic evidence (x-ray or radiologist's report) fulfilling the Modified New York criteria for AS [redacted]
4. Active AS assessed by total BASDAI of ≥ 4 (NRS of 0-10) at baseline
5. Spinal pain as measured by BASDAI question #2 of ≥ 4 (NRS of 0-10) at baseline
6. Total back pain of ≥ 4 on a NRS of 0-10 at baseline
7. Patients should have been on NSAIDs at the maximum tolerated dose for at least 4 weeks prior to their Baseline Visit, with an inadequate response or for less than 4 weeks if withdrawn for intolerance, toxicity or contraindications
8. Patients who are regularly taking NSAIDs (including COX-1 or COX-2 inhibitors) as part of their AS therapy are required to be on a stable dose for at least 2 weeks before their Baseline Visit
9. Patients who have been on a TNFα inhibitor (not more than one) must have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months prior to baseline or had been intolerant upon administration of an anti-TNFα agent
10. Patients who have previously been on a TNFα inhibitor will be allowed entry into study after appropriate wash-out period prior to their Baseline Visit:
    - 4 weeks for Enbrel® (etanercept) – with a terminal half-life of 102 ± 30 hours (s.c. route)
    - 8 weeks for Remicade (infliximab) – with a terminal half-life of 8.0-9.5 days (i.v. infusion)
    - 11 weeks for Humira (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks)(s.c. route)
    - 11 weeks for Simponi (golimumab) – with a terminal half-life of 11-14 days
    - 11 weeks for Cimzia (certolizumab) – with a terminal half-life of 14 days
11. Patients taking MTX (≤ 25 mg/week), sulfasalazine (≤ 3 g/day), or leflunomide (≤20 mg/day) are allowed to continue their medication and must have taken it for at least 2 months and have to be on a stable dose for at least 4 weeks prior to baseline
12. Patients on MTX must be on a stable folic acid supplementation before their Baseline Visit.
13. Patients who are on a DMARD other than MTX, sulfasalazine or leflunomide must discontinue the DMARD 4 weeks prior to baseline
14. Patients taking systemic corticosteroids have to be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before baseline

4.2 Exclusion Criteria

Patients fulfilling any of the following criteria during the Screening Period or at the Baseline Visit 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/subjects.

1. Patients with total ankylosis of the spine
2. Use of other investigational drugs within 5 half-lives of enrollment, or within 4 weeks before the Baseline Visit, whichever is longer
3. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes
4. Chest x-ray, CT scan, or chest magnetic resonance imaging (MRI) with evidence of ongoing infectious or malignant process, obtained within 3 months prior to screening and evaluated by a qualified physician
5. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17, IL-12/23, or the IL-17 receptor, or any other biologic immunomodulating agent, except those targeting TNFα
6. Patients who have taken more than one anti-TNFα agent
7. Any intramuscular or intravenous corticosteroid injection within 2 weeks before baseline
8. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before baseline
9. 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)
10. Patients taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine)
11. Active systemic infections during the last two weeks (exception: common cold) prior to baseline
12. Active ongoing inflammatory diseases other than AS that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease or uveitis
13. 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
14. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension, congestive heart failure (New York Heart Association status of class III or IV), uncontrolled diabetes, or very poor functional status unable to perform self-care
15. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria:
    - Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/baseline, to rule out lab error
16. Serum creatinine level exceeding 2.0 mg/dL (176.8 µmol/L) at screening
17. Screening total WBC count < 3,000/µL, or platelets < 100,000/µL or neutrophils <1,500/µL or hemoglobin < 8.5 g/dL (85 g/L)

18. Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening
19. 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)
20. Patients with other clinically significant conditions (not associated with the study indication) which in the judgement of the investigator might interfere with the assessment of this study, or puts the subject at increased risk
21. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)
22. Inability or unwillingness to receive injections with the PFS
23. 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
24. Donation or loss of 400 mL or more of blood within 8 weeks before baseline
25. History or evidence of ongoing alcohol or drug abuse, within the last 6 months before baseline
26. Patients who know they will be unable to complete 1 year of study treatment period
27. Administration of live vaccines during the study period or 6 weeks prior to baseline
28. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5 mm or according to local practice/guidelines) or a positive central laboratory TB blood screening test as indicated in the assessment schedule in Table 6-1. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment according to local country guidelines must have been initiated
29. 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
30. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, are excluded from the study unless they are using highly effective methods of contraception during dosing and for 16 weeks after stopping of study medication. All women of child-bearing potential must have a negative serum pregnancy test at Screening Visit 2, regardless of the method of contraception being used. Highly 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 six weeks before taking study

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).
- 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 study drug.

NOTE: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Novartis will supply the following study treatments in packaging of identical appearance:

- Secukinumab 150 mg provided in 1.0 mL in a prefilled syringe (PFS) for s.c. injection.
- Secukinumab placebo provided in 1.0 mL a PFS for s.c. injection (for matching 150 mg dose to blind 300 mg dosing)

NOTE: The PFS are packed in an open-label fashion from baseline through the Week 12 visit. Beginning Week 16, the PFS are packed in a double-blinded fashion for the remainder of the study.

5.1.2 Additional treatment

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

5.2 Treatment arms

Treatment Period 1

Once screening has been completed and patients have met the eligibility criteria, all patients will undergo 16 weeks of open-label treatment with secukinumab 150 mg s.c. self-administered at the site at baseline, Weeks 1, 2, 3, 4, 8, and 12.

All assessments at the scheduled visit will be performed before the patients receive the injection with the appropriate study medication for that visit.

At Week 12 and Week 16, all patients will be assessed for achieving the ASDAS inactive disease (<1.3) status, as well as for an inadequate response or a non-response. Patients will then be divided into three groups:

1. Responders: Patients achieving ASDAS inactive disease (total score < 1.3) status at Week 12 and Week 16 and who do achieve a decrease (improvement) from baseline in total ASDAS score at both Week 12 and Week 16.

2. Inadequate responders: Patients who have active disease, defined as an ASDAS total score of ≥1.3 at either Week 12 or Week 16, and who do achieve a decrease (improvement) from baseline in total ASDAS score at both Week 12 and Week 16.

3. Non-responders: Patients who exhibit no change or an increase (worsening) from baseline in total ASDAS score at either Week 12 or Week 16

Treatment Period 2 (Responders and Non-responders)

Responders: Patients achieving responder status will enter Treatment Period 2 and continue to receive 150 mg s.c. (one s.c. injection of secukinumab 150 mg) at Weeks 16, 20, 24, 28, 32, 36, 40, 44, and 48, as well as one matched placebo dose (s.c. injection) to maintain the integrity of the blind for the randomized Inadequate Responder group. This Responder group will be evaluated for maintenance of ASDAS inactive disease while remaining on 150 mg of secukinumab. All assessments at the scheduled visit will be performed before the patients receive the injection with the appropriate study medication for that visit.

NOTE: To minimize patient burden, at the Week 16 visit, the hs-CRP measurement that is part of the ASDAS calculation will be imputed from the Week 12 hs-CRP results to allow for assignment into the groups above. Historically, hs-CRP levels have varied little between Week 12 and Week 16 in previous studies of secukinumab in active AS.

Non-responders: Nonresponders will terminate the study at Week 16.

Treatment Period 2 (Inadequate Responders)

Inadequate responders will be randomized via the Interactive Response Technology (IRT) system in a 1:1 ratio to receive either secukinumab 300 mg (two s.c. injections of the 150 mg dose) or secukinumab 150 mg (one s.c. injection of the 150 mg dose and one s.c. injection of placebo) at Weeks 16, 20, 24, 28, 32, 36, 40, 44, and 48.

Patients will self-administer all secukinumab doses up to Week 48 after they have received training by the site to self-administer their secukinumab dose. While patients are encouraged to self-inject, continued assistance by the site or home nurse is acceptable. All assessments at the scheduled visit will be performed before the patients receive the injection with the appropriate study medication for that visit.

5.3 Treatment assignment and randomization

At Baseline through Week 12, the Interactive Response Technology (IRT) system will be used at each visit to dispense open-label treatment to enrolled patients. The system will specify unique medication numbers that will correspond to open-label treatment to be dispensed.

Responders: At Week 16 through Week 48, the IRT system will be used at each visit to dispense treatment and matching placebo to ASDAS-inactive disease responders. The system will specify unique medication numbers that will correspond to treatment to be dispensed.

Inadequate Responders: At Week 16, all ASDAS-inactive disease inadequate responder eligible patients will be randomized via IRT to one of the treatment groups in a ratio of 1:1 (secukinumab 300 mg or secukinumab 150 mg). The IRT system will assign a randomization number to the subject, which will be used to link the subject to a treatment group in the system and will specify unique medication numbers for treatment to be dispensed to the subject. The randomization number will not be communicated to any of the site staff. The IRT system will be used at each visit from Week 16 through Week 48 to dispense treatment.

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

Randomization will be stratified by TNF-alpha inhibitor status (naive, inadequate responder). The stratification ensures balanced allocation of patients to treatment groups within the TNF-alpha inhibitor status strata.

The randomization scheme for patients will be reviewed and approved by a member of the Novartis Biometrics group.

5.4 Treatment Blinding

Patients, investigators/site staff, persons performing assessments, and Novartis study personnel will remain blinded to individual treatment assignment from the time of randomization (Week 16) for the inadequate responder group and responder group until the final database lock using the following methods:

1. Randomization data will be kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:

- Specific vendors whose role in trial conduct requires their unblinding (e.g., IRT system)
- Drug Supply Management (DSM);

2. The identity of secukinumab and placebo prefilled syringes (PFS) will be concealed by identical packaging, labeling, schedule of administration, and appearance.

There will be a database lock after all patients have completed the Week 52 visit and data are clean and complete.

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

5.5 Treating the patient

5.5.1 Patient numbering

Each subject is uniquely identified in the study by a combination of his/her four digit center number and three digit subject number. The center number is assigned by Novartis to the investigative site. After the subject has signed the ICF, the investigator or his/her staff will contact the IRT system and provide the requested identifying information for the subject to register them into the IRT system. The site must select the CRF book with a matching Patient Number from the EDC system to enter data. At each site, the subjects are numbered sequentially. (e.g. the first subject is assigned subject number 001, and subsequent patients are assigned consecutive numbers; the second subject is assigned subject number 002; the third subject is assigned subject number 003). Once assigned to a subject, a subject number will not be reused. If the subject fails to be randomized for any reason, the IRT system must be notified within 2 days and the reason for not being randomized will be entered on the Screening Phase Disposition Form within the eCRF. The appropriate eCRF(s) pages should also be completed.

5.5.2 Dispensing the study drug

All doses of study treatment will be self-administered by patients at the study site (or at home) after they have received training by the site on how to self-administer.

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

specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in English and comply with legal requirements in the U.S. 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 their outer box must be stored in a 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 investigational medicinal products and local regulations.

The Investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

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.

Destruction of the unused drug should be done according to local requirements and after approval by Novartis clinical team.

5.5.3.2 Handling of additional treatment

5.5.4 Instructions for prescribing and taking study treatment

All study treatment will be self-administered subcutaneously after visit study assessments have been completed. Qualified staff will administer the injection only to those patients who are not able to self-administer the PFS injection. Detailed instructions on the self-administration of the study treatment will be described in the Instructions For Use (IFU) and provided to each subject.

The first study treatment administration will occur at the Baseline Visit **after** inclusion/exclusion criteria have been confirmed, all study scheduled assessments have been performed, and the scheduled blood samples have been drawn.

The patient will be instructed by the site staff, utilizing the IFU, on how to self-inject via PFS. Patients will be asked to raise any questions, if they have any, and then to proceed with self - injection. Self-injection will take place under the supervision of a site staff member. At the Week 1 and subsequent visits, patients will be asked to refer to the IFU and to proceed with self-injection of the study drug. While patients are encouraged to self-inject, continued assistance by the site or home nurse is acceptable.

Study treatment will be administered weekly following the baseline dose (Weeks 1, 2, 3, and 4) and every 4 weeks thereafter (at Week 8 until Week 48).

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

The Investigator should promote compliance by instructing the subject to attend the study visits as scheduled and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject should be instructed to contact the Investigator if he/she is unable for any reason to attend a study visit as scheduled or if he/she is unable for any reason to take the study treatment as prescribed. For patients unable to travel to the clinic for their study visit, flexible study visits (home nursing study visits) and telemedicine/telephone visits with direct to patient shipment of study drug are alternative options for all post-Baseline study visits. For more information regarding flexible study visits, please refer to the Site Manual for Home Visits (Flexible Study Visits).

5.5.4.1 Administration

Secukinumab Solution for Subcutaneous Injection (active or placebo, respectively) will be provided in prefilled syringes (PFS).

Single syringes will be packed in individual boxes. The boxes containing the safety prefilled syringes with study treatment solution should be kept at 2 to 8°C (36°F and 46°F) and protected from light. Prior to administration the boxes containing the safety prefilled syringes with study treatment solution should be allowed to come to room temperature unopened for about 20 minutes before administration. Used safety syringe should be disposed immediately after use in a sharps container.

Patients will be instructed at baseline by the site staff on how to self-inject either secukinumab or placebo (blinded) via PFS following the IFU. After the Baseline Visit, 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. Each new injection should be given at least one inch from the previously used site. If subject chooses the abdomen, 2 inches area around navel should be avoided. Investigational drug should not be injected into areas where the skin is tender, bruised, red, or hard, or where subject has scars or stretch marks. Injection sites should be changed to reduce the risk of reaction.

All study treatment will be self-administered subcutaneously after visit study assessments have been completed. While patients are encouraged to self-inject, continued assistance by the site or home nurse is acceptable.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments are not permitted.

Study treatment interruptions are not permitted with the following exceptions:

- If, in the opinion of the investigator, a subject is deemed to be placed at a significant safety risk unless dosing is temporarily interrupted. In such cases study treatment should be interrupted only during the time that this risk is present and ongoing. Study treatment can be restarted at the next scheduled visit after resolution of the safety risk.
- The effect of secukinumab on live vaccines is unknown; therefore live vaccines should not be administered during participation in the study. In case a live vaccine has been administered due to a medical urgency, the subject **must** be discontinued from study treatment as per Section 5.6.2. Non-live vaccinations are permitted during the study.

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

5.5.6 Rescue medication

Rescue medication is not permitted during the study. Patients will be free to discontinue participation in the study at any time.

5.5.7 Concomitant medication

Patients should be instructed to notify the study site about any new medications he/she takes after being 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 appropriate eCRF.

Guidelines for the use of specific medications are provided below:

Methotrexate (MTX)

Patients taking MTX (up to 25 mg/week) must be on a stable dose for at least 4 weeks before the Baseline Visit and maintained stable throughout the duration of the study.

Folic acid

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

Sulfasalazine

Subjects taking sulfasalazine (≤ 3 g/day) must be on a stable dose for at least 4 weeks before the Baseline Visit and maintained stable throughout the duration of the study.

Leflunomide

Subjects taking luflunomide (≤ 20 mg/day) must be on a stable dose for at least 4 weeks before the Baseline Visit and maintained stable throughout the duration of the study.

Low Strength opioids

Subjects are allowed to take low strength opioids PRN. However, patients should not take a dose of low strength opioids within 24 hours of a study visit. High potency opioid analgesics (e.g., methadone, hydromorphone, morphine) are prohibited in this study.

Systemic corticosteroids

Treatment with systemic corticosteroids is permitted up to a maximum daily dosage of 10 mg prednisone equivalent and the dose is stable within the 2 weeks preceding the Baseline Visit. The subject should remain on a stable dose throughout the duration of the study.

Higher-dose, time-limited corticosteroid courses (bursts) may be permitted for exacerbations of medical conditions unrelated to AS (e.g., asthma, chronic obstructive pulmonary disease (COPD), contact dermatitis) after baseline. Any change in the dose of systemic corticosteroids during the trial must be recorded on the corresponding CRF.

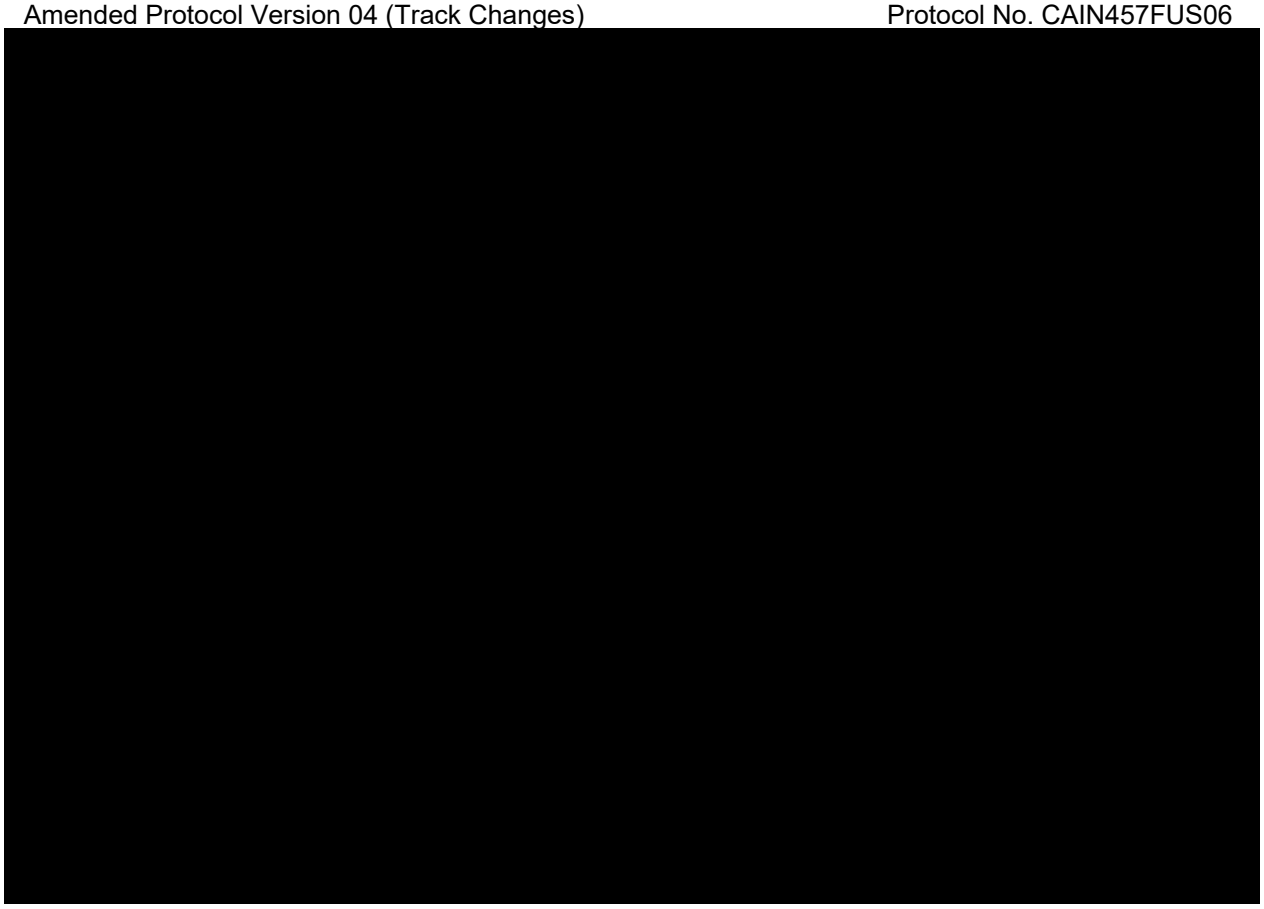
Intra-articular corticosteroids are not permitted within the 4 weeks preceding the Baseline Visit and up to Week 52.

Non-steroidal anti-inflammatory drugs (NSAIDs) (including COX-1 or COX-2 inhibitors) and acetaminophen

Patients on regular use of NSAIDs or acetaminophen should be on stable dose for at least 2 weeks before the Baseline Visit to allow inclusion in the study. They should remain on stable dose in the study up to Week 52.

Subjects taking NSAIDs or acetaminophen PRN within the 2 weeks before baseline can continue to do so in the study; however, they have to refrain from any intake during the 24 hours before a visit.

Any change of the NSAIDs or acetaminophen treatment during the trial should be recorded on the corresponding eCRF page



5.5.9 Emergency breaking of assigned treatment code

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study 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 system. When the Investigator contacts the IRT 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 confirmation via email and/or fax. The system will automatically inform the Novartis monitor for the site and the Clinical Trial Lead (CTL) that the code has been broken.

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

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

The last scheduled administration of therapy will be at Visit 18/Week 48. A subject's study participation is completed once Visit 19/Week 52 has been completed. After this date, any SAEs that occur in the following 30 days must be reported. The investigator will also follow any AEs for which there is no outcome that can be reported at the final study visit. Pregnancies will be followed until the outcome of the pregnancy is known.

Information on the subject's completion or discontinuation of the study and the reason for discontinuation of the study will be recorded on the corresponding CRFs.

In any case, the investigator or site staff must contact the IRT system as soon as possible to record the subject's study completion (Week 52) and/or withdrawal from the trial.

The study as a whole will be completed once all enrolled patients have completed the study per the protocol and the clinical database has been locked. Recruitment into the study will be terminated by the sponsor once the targeted number of randomized patients has been met or is foreseen to be met with the patients already in screening. Patients who have been screened and have a screening visit recorded in the IRT system at the time that the planned enrollment number is met will be allowed to enter the trial and to be randomized if they are eligible.

Upon completion of study participation, patients will return to individual medical treatment, as determined by their treating physician.

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

5.6.2 Discontinuation of study treatment

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

Study treatment must be discontinued if the investigator determines that continuation of study treatment would result in a significant safety risk for a subject. **Patients that discontinue study treatment cannot continue in the trial. They must be discontinued from the trial altogether.**

The following circumstances **require** study treatment discontinuation and consequently discontinuation from the trial:

- Withdrawal of informed consent
- Emergence of the following adverse events:
  a. Any severe or serious adverse event that in the judgment of the investigator/qualified site staff, taking into account the subject's overall status, prevent the subject from continuing study treatment;
  b. Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the subject at a safety risk for continuation in the study (A general guidance on clinically notable laboratory values is provided in [redacted].

c. Life-threatening infection

- Pregnancy;
- [redacted]
- Emergency unblinding
- Patient refusal to complete PRO questionnaires at Baseline, Week 12 or Week 16
- Any other protocol deviation that results in a significant risk to the subject's safety;

For any subject whose treatment code has been broken inadvertently for any reason, the appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued.

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

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

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 occurs only 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.

If premature withdrawal occurs for any reason, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient source and on the appropriate study completion eCRF.

Patients who withdraw consent should return for an End of Study Visit (see Table 6-1). The End of Study Visit should be scheduled approximately four weeks after the last study treatment, and should be performed before any new treatment is initiated. After the End of Study Visit, any SAEs that occur in the following 30 days must be reported. The investigator will also follow any AEs for which there is no outcome that can be reported at the final study visit. Pregnancies will be followed until the outcome of the pregnancy is known.

Patients who are prematurely withdrawn from the study will not be replaced by newly enrolled patients.

5.6.4 Loss to follow-up

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

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 enrollment). Should this be necessary, the subject should be seen as soon as possible and treated as a prematurely withdrawn as described in Section 5.6.2. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing Institutional Review Board/Independent Ethics Committee (IRBs/ECs) 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. Assessments that will only be reported in the source documentation are marked with an 'S'.

Patients/subjects must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. For patients unable to travel to the clinic for their study visit, flexible study visits (home nursing study visits) and telemedicine/telephone visits with direct to patient shipment of study drug are alternative options for all post-Baseline study visits. For more information regarding flexible study visits, please refer to the Site Manual for Home Visits (Flexible Study Visits).Patients who prematurely discontinue the study for any reason should be scheduled for an End of Study Visit as soon as possible, at which time all of the assessments listed will be performed. At this End of Study Visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

If patients do not have a chest X-ray available within 3 months of screening, the X-ray should be performed only after it is certain the subject meets inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation.

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

Screening will be flexible in duration based on the time required to be evaluated for eligibility. Sufficient time is allowed for potential medication washout, in addition to all other assessments indicated in Table 6-1. Upon the completion of screening and confirmation that all inclusion and none of the exclusion criteria have been met, the subject may begin the Baseline Visit.

Screening will consist of two consecutive visits. During Screening Visit 1 (SV1) and Screening Visit 2 (SV2), initial assessments will be performed as outlined in Table 6-1. [redacted]

Patients who may be eligible for Screening Visit 2 immediately following Screening Visit 1 should have at least one week in between these two screening visits.

Premature Discontinuation

For patients who discontinue study treatment prematurely for any reason after baseline, an End of Study Visit must be performed approximately four weeks after the last dose of study treatment. In accordance with SAE reporting guidelines, any SAEs reported in the 30 days after the End of Study Visit, regardless of causality, must be reported to Novartis within 24 hours of learning of its occurrence and recorded in the eCRF.

Documentation of attempts to contact the subject should be recorded in the source documentation.

Unscheduled visits

Patients may be seen at any time for an unscheduled visit, e.g., if they experience deterioration or AEs that in the opinion of the investigator/qualified site staff need intervention or repeat laboratory testing. The assessment(s) performed at an unscheduled visit must include at minimum: an assessment of concomitant medication and procedures/significant non-drug therapies, vital signs, and an AE/SAE assessment. Any additional assessments performed are at the investigator/qualified site staff's discretion. During an unscheduled visit, study treatment will not be administered.

Table 6-1 Assessment schedule

Period	SCR[1]		Treatment Period 1 (Open-Label)								Treatment Period 2 (Double-Blind or Open-Label)									Telemedicine/ telephone visit	Unscheduled	Notes
Week	-13 to -3	-2 to BL	BL	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52/Study Completion/ EOS[2]			
Visit No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19			
Assessments																						
Obtain informed consent	X																					See section 10.2
Inclusion / exclusion criteria	X	X	X																			See sections 4.1 – 4.2
Demographics	X																					See section 6.3
General Medical history / previous therapies	X																					See section 6.3
Relevant AS medical history / current medical conditions	X																					See section 6.3
Washout evaluation / instruction	S																					See Table 5-1
Modified NY criteria	S	S	S																			See section 13.2
Radiologic evidence (x-ray) to central reader		X																				See section 6.6.9

Period	SCR[1]		Treatment Period 1 (Open-Label)								Treatment Period 2 (Double-Blind or Open-Label)									Telemedicine/ telephone visit	Unscheduled	Notes
Week	**-13 to -3**	**-2 to BL**	**BL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/Study Completion/ EOS[2]**			
Visit No	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**			
Assessments																						
Smoking and alcohol history			X																			See section 6.3
Cardiovascular medical history	X																					See section 6.3
Physical Exam[3]		S	S				S	S	S	S	S	S	S	S	S	S	S	S	S			See section 6.6.4
Weight		X	X							X									X			See section 6.6.6
Height		X																				See section 6.6.6
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	See section 6.6.5
Chest X-ray		X																				See section 6.6.2
ECG		X																				See section 6.6.3
Prior/ Concomitant medication/ non-drug therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See section 5.5.7

Period	SCR[1]		Treatment Period 1 (Open-Label)								Treatment Period 2 (Double-Blind or Open-Label)											
Week	**-13 to -3**	**-2 to BL**	**BL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/Study Completion/ EOS[2]**	**Telemedicine/ telephone visit**	**Unscheduled**	**Notes**
Visit No	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**			
Assessments																						
IRT transaction	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	X		See section 5.3
Administration of s.c. study treatment via PFS			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		See section 5.5.4
Adverse Events/SAEs (inc. injection site reaction & occurrence of infections)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See section 7.1 – 7.2
QuantiFERON TB-Gold test		X																				See section 6.6.1
Hematology, blood chemistry[4]		X	X						X	X			X			X			X			See section 6.6.7.1 - 6.6.7.2
Serum pregnancy test		X																				See section 6.6.8
Urinalysis/Urine pregnancy test			X				X		X	X		X		X		X			X			See section 6.6.7.3 and 6.6.8
[redacted]																						
HLA-B27		X																				See section 6.6.7.4

Period	SCR[1]		Treatment Period 1 (Open-Label)								Treatment Period 2 (Double-Blind or Open-Label)											
Week	-13 to -3	-2 to BL	BL	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52/Study Completion/ EOS[2]	Telemedicine/ telephone visit	Unscheduled	Notes
Visit No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19			
Assessments																						
Responder status assessment										X										X		See section 3.1
BASDAI	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		See section 6.5.2.7
[redacted]																						
Patient's global assessment of disease activity	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		See section 6.5.2.4
[redacted]																						
[redacted]																						
ASAS-HI			X				X	X	X	X	X	X	X	X	X	X	X	X	X	X		See section 6.5.4
FACIT-Fatigue v4			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		See section 6.5.6
[redacted]																						

Period	SCR[1]		Treatment Period 1 (Open-Label)								Treatment Period 2 (Double-Blind or Open-Label)									Telemedicine/ telephone visit	Unscheduled	Notes
Week	-13 to -3	-2 to BL	BL	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52/Study Completion/ EOS[2]			
Visit No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19			
Assessments																						
[redacted]																						
Treatment period 1 completion form										X										X		
Treatment period 2 completion form																			X	X		

[redacted]

[2] Patients who discontinue prematurely or withdraw consent should return for an End of Study Visit. The End of Study Visit should be scheduled approximately four (4) weeks after the last study treatment and should be performed before any new treatment is initiated.

[3] The Physical Exam is documented in the source; not in the database. If flexible study visits are permitted, a limited physical assessment will be performed by the home nurse in place of a complete physical examination.

[4] Fasting sample

[5] Measures captured only for TNF inhibitor inadequate responders currently on a TNF inhibitor and prior to discontinuation/washout.

6.1 Rescreening

Rescreening may be allowed under certain conditions. Requests from the investigator/site staff to rescreen patients will be handled on a case-by-case basis with Medical Director approval required before proceeding with the rescreening. Rescreening cannot be done if the patient previously entered Treatment Period 1 or Treatment Period 2.

If a patient rescreens for the study, the patient must sign a new ICF and be issued a new patient number prior to any screening assessments being conducted under the new patient number. The date of the new informed consent signature must be entered in the Informed Consent eCRF corresponding to the new patient number.

For rescreening, all screening assessments must be performed per protocol, except the tuberculosis (TB) work up (if applicable). If the date of the TB work up is less than 12 weeks from the projected baseline date, then it is not required that the TB work up be repeated; however, the rescreened patient MUST repeat the QuantiFERON test performed by the central laboratory.

6.2 Information to be collected on screening failures

All patients who sign informed consent but discontinue prior to the Baseline Visit at Visit 3 are considered screening failures. The IRT system must be notified about the discontinuation, and the primary reason for the screen failure should be entered in the Screening Phase Disposition eCRF.

In addition, only the following eCRFs should be completed: Demography eCRF, Informed Consent eCRF, Inclusion/Exclusion eCRF, and the adverse event (AE) eCRF should be completed for any Serious Adverse Events (SAEs) that occurred during the Screening Period. Adverse events that are not serious will be followed by the investigator and collected only in the source data.

6.3 Patient demographics/other baseline characteristics

At Screening Visit 1, subject demographic and baseline characteristic data to be collected on all subjects and to be recorded in the CRF include:

- Age, sex, race, ethnicity
- Relevant AS and general medical history/current medical condition data until the start of investigational treatment: date of AS symptom onset (specifically axial symptom onset in the back, buttock or hip pain), date of AS diagnosis, targeted medical history events related to AS, such as the history of extra-axial involvement (uveitis, psoriasis, inflammatory bowel disease, enthesitis, peripheral arthritis), number of previous DMARDs used, previous AS therapies, functional status class according to New York criteria, cardiovascular medical history and smoking history.

Where possible, diagnoses and not symptoms will be recorded.

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

6.4 Treatment exposure and compliance

All dates and times of study treatment administration will be recorded on the appropriate CRF. Drugs administered prior to start of treatment and other drugs/procedures continuing or started during the study treatment period will be entered in the appropriate CRF.

Compliance is expected to be 100%, unless temporary interruption is needed for safety reasons as described in Section 5.5.5. Compliance will be assessed by a field monitor using

information provided by the subject and the authorized site personnel. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.5 Efficacy

- Ankylosing Spondylitis Disease Activity Score (ASDAS) and ASDAS response categories
- Assessment of Spondyloarthritis International Society criteria (ASAS)
- Patient's global assessment of disease activity
- Patient's assessment of back pain intensity
- [redacted]
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- [redacted]
- ASAS-Health Index (ASAS-HI)
- [redacted]
- FACIT- Fatigue

All efficacy assessments should be performed prior to administration of study treatment. Details relating to the administration of all PROs are provided in Appendix 4.

6.5.1 ASDAS and ASDAS response categories

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite index to assess disease activity in AS. The ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score) will be utilized to assess the disease activity status. Parameters used for the ASDAS calculation include:

1. Spinal pain (BASDAI question 2),
2. The patient's global assessment of disease activity,
3. Peripheral pain/swelling (BASDAI question 3),
4. Duration of morning stiffness (BASDAI question 6) and
5. C-reactive protein (CRP) in mg/L (Sieper 2009, Lukas 2009).

Disease activity states are inactive disease, moderate disease activity, high disease activity, and very high disease activity. The 3 values selected to separate these states were:

- < 1.3 between inactive disease and moderate disease activity,
- < 2.1 between moderate disease activity and high disease activity, and
- 3.5 between high disease activity and very high disease activity.

Selected cutoffs for improvement scores were a change ≥ 1.1 unit for "clinically important improvement" and a change ≥ 2.0 units for "major improvement" (Machado 2011).

6.5.2 Assessment of Spondylo-Arthritis International Society criteria (ASAS)

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

ASAS domains:

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

6.5.2.1 ASAS Responder Criteria 20% (ASAS20)

ASAS 20 response is defined as an improvement of ≥ 20% and ≥ 1 unit on a scale of 10 in at least three of the four domains and no worsening of ≥ 20% and ≥ 1 unit on a scale of 10 in the remaining domain. Assessments will be made relative to patient's baseline values.

6.5.2.2 ASAS Responder Criteria 40% (ASAS40)

ASAS 40 response is defined as an improvement of ≥ 40% and ≥ 2 units on a scale of 10 in at least three of the four domains and no worsening at all in the remaining domain. Assessments will be made relative to patient's baseline values.

6.5.2.3 ASAS partial remission criteria

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

[redacted]

[redacted]

[redacted]

6.5.2.7 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI will be completed at Visits 2 – 19. It consists of a 0 through 10 scale (0 being no problem and 10 being the worst problem, captured using a NRS), which is used to answer 6 questions pertaining to the 5 major symptoms of AS:

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

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

[redacted]

6.5.4 ASAS Health Index (ASAS-HI)

The ASAS-HI is administered at Visit 3 and Visits 7 – 19. It is a self-administered questionnaire and measures functioning and health over 17 aspects of health and 9 environmental factors in patients with spondyloarthritis. Items include pain, maintaining a body position, moving around, toileting, energy/drive, motivation, sexual functions, driving, community life, handling stress, recreation/leisure, emotional functions, washing oneself, economic self-sufficiency, and sleep. Patients score each item as "I agree" and "I do not agree".

[redacted]

6.5.6 Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue)

The FACIT-Fatigue© is a 13-item questionnaire (Cella 1993; Yellen 1997) that assesses self-reported fatigue and its impact upon daily activities and function. It is administered at Visits 3 – 19.

6.5.7 Appropriateness of efficacy assessments

The efficacy outcome measures used in this study are the standard measures used across all ankylosing spondylitis studies.

6.6 Safety

Safety assessments will consist of evaluating all AEs and SAEs including injection site reactions, ECGs, physical examination, vital signs and laboratory assessments, and assessment of anti-secukinumab antibody development (immunogenicity).

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.

- Determination of tuberculosis status
- Chest X-ray
- Electrocardiogram
- Physical examination
- Vital signs
- Height and weight
- Laboratory evaluations (Hematology, Clinical Chemistry, LFTs, Urinalysis)
- Pregnancy and assessment of fertility
- Tolerability of secukinumab
- Local tolerability (Injection site reactions)
- Evaluation of AE/ SAE's

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.

6.6.1 Determination of tuberculosis status

Determination of tuberculosis (TB) status will be required before administration of study treatment. TB status must be determined by medical history, signs, symptoms, and TB testing (QuantiFERON-TB Gold assay). **If the QuantiFERON-TB Gold Assay test is positive or indeterminate, a TB workup should be performed as defined by local guidelines to determine the subject's TB status.**

QuantiFERON TB-Gold In-Tube assay

A QuantiFERON® TB-Gold In-Tube assay will be performed to assess the TB status at screening for all patients. This test will only be used to determine subject's eligibility for the trial. The test will be used to screen the subject population for latent tuberculosis infection (Doherty et al 2008).

This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous Bacillus Calmette-Guérin vaccination or exposure to other Mycobacteria species.

This test, in contrast to the purified protein derivative (PPD) skin test, is also insensitive to a booster effect since the subject is not exposed to the vaccine. The assay measures the production of interferon-gamma and presents it relative to a negative and a positive control sample (Manuel and Kumar 2008)

The QuantiFERON®-TB Gold assay test will be supplied by the central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the Laboratory Manual.

The results of a TB workup for a subject with a positive or indeterminate test must be recorded in the eCRF.

- If the test result is **negative**, the subject may be randomized.
- If the test result is **positive**, the investigator should perform a TB workup for the test result as per local procedures.
- Patients **positive** for latent TB per workup may be randomized to the trial if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration.
- Patients **positive** for active TB per workup are not eligible for the study.
- Patients **negative** for TB (no signs of latent or active TB) per workup may be randomized to the trial.
- If the test result is **indeterminate**, it is **recommended to repeat the test once**. The investigator may decide to skip the repetition of the test and proceed directly to the workup (however this is not recommended). If a TB workup was conducted prior to screening, results from the workup can be used to assess eligibility if the workup was conducted within 12 weeks prior to baseline.
- If the second test is negative, the subject may be randomized.
- If the second test is positive or indeterminate, the investigator should perform a TB workup as per local guidelines. The subject will not be eligible for randomization if: "active tuberculosis is present", or if "latent tuberculosis is present" and is untreated as per local guidelines.

6.6.2 Chest x-ray

A chest X-ray, CT scan, or MRI obtained locally within 3 months prior to screening will be used to determine eligibility. If patients do not have a chest X-ray, CT scan, or MRI available within 3 months prior to screening, a chest X-ray only must be done after it is fairly certain the subject meets the other inclusion/exclusion criteria in order to minimize unnecessary exposure to X-ray radiation for patients.

If the chest X-ray, CT scan, or MRI evaluated by a qualified physician shows evidence of ongoing infection or malignancy and the subject was not treated subsequent to the X-ray (CT scan or MRI), the subject will not be eligible to enter the study.

6.6.3 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as indicated in Table 6-1. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents.

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

Clinically relevant abnormalities noted after the baseline ECG should be reported as AE (see Section 7).

6.6.4 Physical examination

A complete physical examination will be performed by a professionally trained physician or health professional licensed to perform physical examinations and listed on FDA Form 1572, at the scheduled study visits as indicated in Table 6-1.

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

If flexible study visits are permitted, a limited physical assessment will be performed by the home nurse in place of a complete physical examination. For more information regarding flexible study visits, please refer to the Site Manual for Home Visits (Flexible Study Visits).

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.

6.6.5 Vital signs

Vital signs will be assessed at Visits 2 – 19 and will include BP, pulse rate and body temperature measurements. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using a validated device with an appropriately sized cuff.

If possible, vital signs assessments should be performed by the same study site staff member using the same validated device throughout the study.

Clinically notable vital signs are defined in [redacted]

6.6.6 Height and weight

Height (without shoes) will be measured at Screening Visit 2. Body weight (in indoor clothing but without shoes) will be measured at Screening Visit 2 and Visits 3, 10 and 19. If possible, body weight assessments should be performed using the same scale throughout the study. The Body Mass Index will be calculated by the eCRF system.

6.6.7 Laboratory evaluations

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

6.6.7.1 Hematology

Hemoglobin, platelet, red blood cell (RBC), white blood cell (WBC) and differential white blood cell counts will be measured at Screening Visit 2, and Visits 3, 9, 10, 13, 16 and 19.

6.6.7.2 Clinical chemistry

Measured at Screening Visit 2, and Visits 3, 9, 10, 13, 16 and 19, serum chemistry 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.

6.6.7.3 Urinalysis

Urinalysis will be performed at Visits 3, 7, 9, 10, 12, 14, 16 and 19. 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.

6.6.7.4 HLA-B27

HLA-B27 will be performed at Screening Visit 2.

6.6.8 Pregnancy and assessments of fertility

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

A serum β-hCG test will be performed in all women of child bearing potential at Screening Visit 2; and a local urine pregnancy test at Visits 3, 7, 9, 10, 12, 14, 16 and 19. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If positive, the subject must be discontinued from the trial.

6.6.9 Documented radiologic evidence fulfilling the NY criteria for AS

All patients will require a centrally read x-ray at Screening Visit 2. The outcome of the centrally read x-ray will not determine eligibility of the subject. For patients that are post-baseline, the x-ray should be sent to the central reader immediately.

Investigator sites will receive training on the submission process from the central reader. Once training is completed, sites will be expected to implement this requirement.

6.6.10 Tolerability of secukinumab

Tolerability will be assessed by adverse events, laboratory values and injection site reaction.

6.6.11 Local tolerability

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

The assessment of pain, redness, swelling, induration, hemorrhage and itching will be performed by a physician and will be recorded on the appropriate CRF capturing AEs, including the severity (mild, moderate, severe) and the duration of the adverse reaction.

6.6.12 Appropriateness of safety measures

The safety measures used in this study are reliable and relevant standard measures for a biologic in AS. The safety assessments selected are standard and adequate for this indication/subject population. A chest X-ray at screening (or within 3 months prior to screening) is performed to rule out the presence of a pulmonary malignancy or infectious process, in particular tuberculosis. The radiation exposure that results from the chest X-ray safety measurements are estimated to be far below 1 mS. Effective radiation doses under 3 mS (300 mrem), are considered to be minimal risk. Therefore, the radiation exposure in this study involves minimal risk and is necessary to ensure reliable safety measures before the treatment with a biologic.

[redacted]

[redacted]

7 Safety Monitoring

7.1 Adverse events

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

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

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

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

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

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

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- relationship to the study treatment (no/yes)
- duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event [redacted]
- action taken regarding study treatment
- All adverse events should be treated appropriately. Treatment may include one or more of the following:
  - no action taken (i.e. further observation only)

- study treatment temporarily interrupted
- study treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged

- outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal or unknown)

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

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

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

7.2 Serious Adverse Events

7.2.1 Definition of SAE

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (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, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

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

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

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

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to Novartis DS&E as per Section 7.2.1.1.

7.2.1.1 SAE Reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days following the last study visit must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after the 30 day period following the last study visit should only be reported to Novartis safety 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

There has been no safety signal for liver toxicity with secukinumab to date in approximately 13,000 patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the liver. Standard liver function tests will be obtained at regular intervals, but special measures for liver safety monitoring are not planned. For further information on standard liver function tests, see [redacted]

7.4 Renal safety monitoring

There has been no safety signal for nephrotoxicity with secukinumab to date in approximately 13,000 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 containing clinically significant abnormal values (see [redacted] for notable laboratory values) are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined. Standard renal function tests (blood urea nitrogen, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

7.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the appropriate dose medication CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

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

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

7.6 Pregnancy Reporting

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

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

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

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

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to US CFR 21 Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. All 3rd party data will be transferred to database including laboratory and actigraphy data from the Phillips Actiwatch device.

Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

A CRO working on behalf of Novartis will review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. Randomization codes and data about all study drug(s) assigned to the subject will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the IRT 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 study monitor. The code break functionality will remain available until study completion or upon request of Novartis.

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

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

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 management.

8.4 Data monitoring committee

Not required.

8.5 Adjudication committee

Not required.

9 Data analysis

It is planned that the data from all centers that participate in this protocol will be combined, so that an adequate number of patients will be available for analysis.

The analysis will be conducted on all patient data at the time the trial ends.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Upon completion of Treatment Period 1 (Week 16), responders will enter Treatment Period 2 and continue to receive secukinumab 150mg every 4 weeks through Week 48. Inadequate responders will enter Treatment Period 2 and will be randomized (1:1, double-blinded) to secukinumab 300 mg or secukinumab 150 mg very 4 weeks through Week 48. Nonresponders will be discontinued from the study at Week 16.

Efficacy, safety, and other data from Treatment Period 1, randomized Treatment Period 2 for inadequate responders, and blinded Treatment Period 2 for responders will be summarized. For continuous variables, summary statistics (mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum) at each time point and for change from baseline to Week 16, and change from Week 16 to each time point by treatment group will be reported. For discrete variables, frequency counts and percentages at each time point will be reported by treatment group.

9.1 Analysis sets

The following analysis sets will be used for the statistical reporting and analyses:

Enrolled Set: The Enrolled Set consists of all enrolled patients for the initial 16-week, Treatment Period 1.

Responder Set: The Responder Set consists of all patients who are labeled as responders at the end of Treatment Period 1, and enter Treatment Period 2 receiving blinded secukinumab 150 mg every 4 weeks through Week 48.

Randomized Set: The Randomized Set consists of all randomized patients.

Safety Set: The Safety Set includes all patients who received at least one dose of study treatment during Treatment Period 2. Patients will be analyzed according to the study treatment received.

Full Analysis Set: The Full Analysis Set comprises all patients to whom study treatment has been assigned by randomization. Patients inappropriately randomized (e.g., IRT was called in error for randomization of a screen failed patient) will be excluded from this analysis set. According to the intent-to-treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

9.2 Patient demographics and other baseline characteristics

Demographic and other baseline data, including disease characteristics, will be listed and summarized descriptively for the Enrolled Set, for the Responder Set, and by treatment group for the Full Analysis Set and Safety Set.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, for the Enrolled Set, for the Responder Set, and by treatment group for the Safety Set.

9.3 Treatments

The duration of exposure (in days) will be summarized by means of descriptive statistics for the Enrolled Set, for the Responder Set, and for each treatment group for the Safety Set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, for the Enrolled Set, for the Responder Set, and by treatment group for the Safety Set.

9.4 Analysis of the primary variable(s)

9.4.1 Primary variable(s)

The primary efficacy variable is the ASDAS inactive disease response (yes, no). The primary analysis time point is at Week 52.

9.4.2 Statistical model, hypothesis, and method of analysis

Let π_j denote the probability of an ASDAS inactive disease at Week 52 for treatment group j, j = 1, 2, where 1 and 2 correspond to secukinumab 150 mg and secukinumab 300 mg, respectively. Accordingly, $\pi_j/(1 - \pi_j)$ is the odds for treatment group j, j = 1, 2.

The primary efficacy variable will be analyzed at each time point using a logistic regression model with treatment, TNF-alpha inhibitor status (naive, inadequate responder), and baseline body weight as explanatory variables (Stokes, Davis, and Koch, 2012). The odds ratios and 95% confidence intervals for the odds ratios will be reported, based on the fitted model.

The primary analysis of the primary efficacy variable will be based on the Full Analysis Set.

9.4.3 Handling of missing values/censoring/discontinuations

Post-randomization patients who discontinue prematurely for any reason will be considered non-responders from the time they discontinued.

In an additional analysis, missing data for ASDAS inactive disease response will be imputed using multiple imputation.

9.4.4 Sensitivity analyses

A 95% confidence interval for the difference between the two treatment groups in the proportion of patients who have ASDAS inactive disease will be calculated using the normal approximation to the binomial distribution for the Full Analysis Set.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The secondary efficacy variables are the following:

1. Reduction in ASDAS ≥ 1.1 from Week 16 (yes, no)
2. Change from Week 16 in total BASDAI
3. BASDAI50 response (yes, no)
4. ASAS20 response (yes, no)
5. ASAS40 response (yes, no)
6. ASAS partial remission (yes, no)
7. Change from Week 16 in ASAS-Health Index
8. Change from Week 16 in FACIT-Fatigue

Analyses of secondary efficacy variables 1 and 3 – 6 at each time point will be similar to the primary and sensitivity analyses of the primary efficacy variable.

Secondary efficacy variables 2, 7, and 8 will be analyzed at each time point by an analysis of covariance model with treatment, Week 16 value, TNF-alpha inhibitor status (naive, inadequate responder), and baseline body weight as explanatory variables. The least squares means of the treatment groups, least squares mean difference, and 95% confidence interval for the difference will be reported, based on the fitted linear model. Missing data will be imputed using the last-observation-carried-forward method. In an additional analysis, missing data will be imputed using multiple imputation.

Analyses of the secondary efficacy variables will be based on the Full Analysis Set.

9.5.2 Safety variables

For safety analyses, the Enrolled Set will be used for Treatment Period 1, and the Safety Set will be used for Treatment Period 2. All listings and tables will be presented for Treatment Period 1, for responders who enter Treatment Period 2, and by treatment group for inadequate responders who are randomized.

Adverse events

All information obtained on adverse events will be displayed by treatment group and patient.

The number (and percentage) of patients with adverse events will be summarized in the following ways:

by treatment, primary system organ class and preferred term;

by treatment, primary system organ class, preferred term and maximum severity;

by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, and other significant adverse events leading to discontinuation.

A patient with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, patient, and visit/time, and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

12-lead ECG

All ECG data will be listed by treatment group, patient and visit/time; abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, patient, and visit/time, and if reference ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

[redacted]

9.7 Interim analyses

No interim analysis is planned.

9.8 Sample size calculation

The sample size was calculated based on the primary efficacy variable (i.e., ASDAS inactive disease response) at Week 52 for the Full Analysis Set. The expected ASDAS inactive disease response rates for secukinumab 300 mg and 150 mg treatment groups at Week 52 are 20% and 10%, respectively (corresponding to an odds ratio of 2.25), partly based on results from AIN457F2310 (MEASURE 2) study. With approximately 97 patients in each treatment group (total of 194 randomized patients), one will be able to estimate the difference between ASDAS inactive disease response rates of the two treatment groups at Week 52 with a "margin of error" (half-width of confidence interval) of 10% (corresponding to a standard error of 5%) for a two-sided 95% confidence interval (Julious and Patterson, 2004; nQuery Advisor 7.0).

It is expected that the study will need to enroll approximately 270 patients for the 16-week open-label period, to randomize approximately 194 patients who do not achieve ASDAS inactive disease status at Week 16 (inadequate responders). This assumes that 10% of the 270 enrolled patients will discontinue during the 16-week open-label period; among the remaining enrolled patients, it is assumed that approximately 10% will be responders, 80% will be inadequate responders, and 10% will be non-responders.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent process

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

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

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

10.3 Responsibilities of the investigator and IRB/IEC

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

10.4 Publication of study protocol and results

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

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 standard operating procedures, and are performed according to written Novartis processes.

11 Protocol adherence

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

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

11.1 Protocol amendments

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

12 References

References are available upon request.

Baeten D, Sieper J, Braun J, et al (2015) Secukinumab, an interleukin-IL17A inhibitor, in ankylosing spondylitis. N Eng J Med; 373:2534-48.

Baraliakos X, Landewe R, Hermann K-G, et al (2005) Inflammation in ankylosing spondylitis: a systematic description of the extent and frequency of acute spinal changes using magnetic resonance imaging. Ann Rheum Dis; 64:730-34.

Baraliakos X, Listing J, Fritz C, et al (2011) Persistent clinical efficacy and safety of infliximab in ankylosing spondylitis after 8 years--early clinical response predicts long-term outcome. Rheumatology; 50:1690-9.

Batmaz, Ibrahim, et al. "Sleep quality and associated factors in ankylosing spondylitis: relationship with disease parameters, psychological status and quality of life." Rheumatology international 33.4 (2013): 1039-1045.

Braun J, Baraliakos X, Deodhar A, Baeten D, Sieper J, Emery P, Readie A, Martin R, Mpofu S, Richards HB (2017) Effect of secukinumab on clinical and radiologic outcomes in ankylosing spondylitis: 2-year results from the randomized phase III MEASURE 1 study. Ann Rheum Dis; 76:1070-1077.

Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein K, Morin C. (2012) The consensus sleep diary: standardizing prospective sleep self-monitoring. SLEEP;35(2):287-302.Cella DF, Tulsky DS, Gray G, et al. (1993) The Functional Assessment of Cancer Therapy (FACT) scale: Development and validation of the general measure. Journal of Clinical Oncology; 11(3):570-9.

Chen KY, Bassett DR (2005) The technology of accelerometry-based activity monitors: current and future. Med Sci Sports Exerc; 37(11 Suppl):S490-500

Cosentyx [package insert] (2016) East Hanover NJ: Novartis.

Deodhar, Atul, Jürgen Braun, Robert D. Inman, Michael Mack, Shreekant Parasuraman, Jacqueline Buchanan, Benjamin Hsu, Tim Gathany, and Désirée Van Der Heijde. "Golimumab reduces sleep disturbance in patients with active ankylosing spondylitis: results from a randomized, placebo-controlled trial." Arthritis care & research 62, no. 9 (2010): 1266-1271.

Doherty SD, Van Voohes A, Lebwohl MG (2008) National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologic agents. J Am Acad Dermatol; 59(2):209-17.

Gladman DD (2007) Axial disease in psoriatic arthritis. Curr Rheumatol Rep; 9:455-60.

Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, et al. (2003) Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis; 62:127-32.

In E, Turgut T, Gulkesen A, Yolbas S, Akgol G, Koca SS (2016) Sleep quality is related to disease activity in patients with ankylosing spondylitis. J Clin Rheumatol; 22(5):248-252

Julious SA, Patterson SD (2004) Sample sizes for estimation in clinical research. Pharmaceutical Statistics; 3:213-215.

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

Lukas C, Landewé R, Sieper J (2009) Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis; 68(1):18-24.

Machado PM, Landewé RB, van der Heijde DM (2011) Endorsement of definitions of disease activity states and improvement scores for the Ankylosing Spondylitis Disease Activity Score: results from OMERACT 10. J Rheum; 38(7):1502-06.

Manuel O, Kumar D (2008) QuantiFERON-TB Gold assay for the diagnosis of latent tuberculosis infection. Expert Rev Diagn; 8(3):247-56.

[redacted]

Marzo-Ortega H, Sieper J, Kivitz A, Blanco R, Cohen M, Martin, R, Readie A, Richards HB, Porter B (2017) Secukinumab and sustained improvement in signs and symptoms of patients with active ankylosing spondylitis through two years: results from a phase III study. Arth Care & Res; 69(7):1020-1029.

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

McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, van der Heijde D, Landewe R, Conaghan PG, Gottlieb A, Richards H, Pricop L, Ligozio G, Patekar M, Mpofu (2015) Lancet; 386:1137-1146.

Nemoto, O., M. Furue, H. Nakagawa, M. Shiramoto, R. Hanada, S. Matsuki, S. Imayama et

al. (2016) The first trial of CIM331, a humanized antihuman interleukin-31 receptor A antibody, in healthy volunteers and patients with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a single dose in a randomized, double-blind, placebo-controlled study. British Journal of Dermatology; 174: 296-304.

Redfield, Margaret M., Kevin J. Anstrom, James A. Levine, Gabe A. Koepp, Barry A.

Borlaug, Horng H. Chen, Martin M. LeWinter et al. (2015) Isosorbide mononitrate in heart failure with preserved ejection fraction. New England Journal of Medicine; 373:2314-2324.

Rudwaleit M, Metter A, Listing J, Sieper J, Braun J. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. Arthritis Rheum 2006; 54: 569–78.

Sieper J, Rudwaleit M, Baraliakos X, et al (2009) The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis.; 68 Suppl 2:ii1-44.

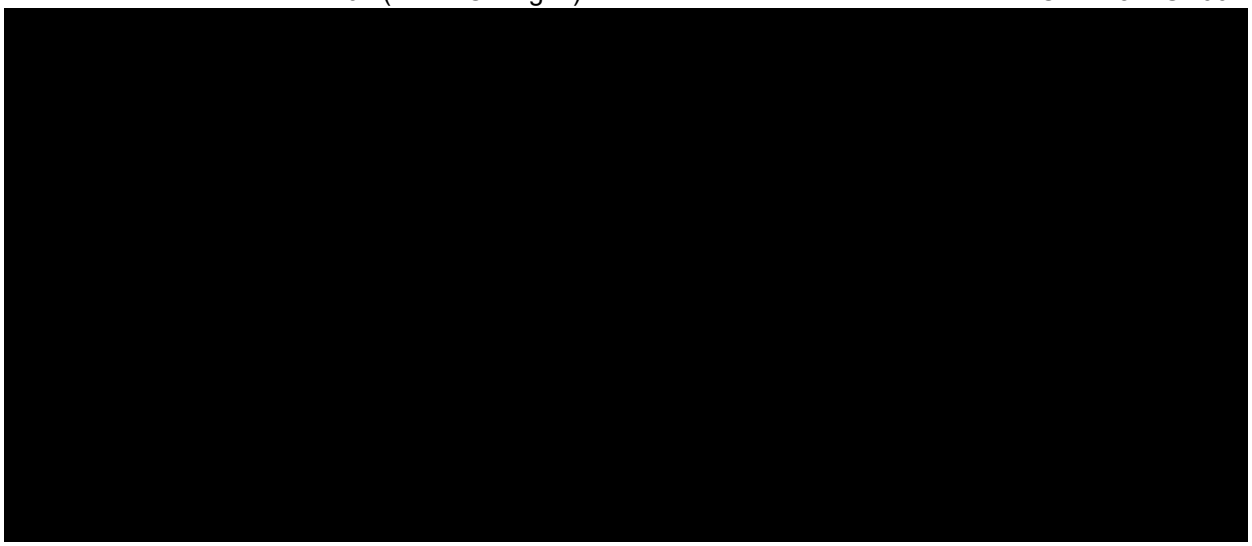
Stokes ME, Davis CS, Koch GG (2012) Categorical data analysis using the SAS system. 3rd ed; Cary, NC: SAS Institute, Inc.

Trudeau J, Van Inwegen R, Eaton T, Bhat G, Paillard F, Ng D, Tan K, Katz NP (2015) Assessment of Pain and Activity Using an Electronic Pain Diary and Actigraphy Device in a Randomized, Placebo-Controlled Crossover Trial of Celecoxib in Osteoarthritis of the Knee. Pain Practice; 15:247-255.

van der Heijde D, Landewe RB, Mease PJ, McInnes IB, Conaghan PG, Pricop L, Ligozio G, Richards HB, Mpofu S (2016) Arth & Rheumatol; 68(8):1914-1921

Yellen SY et al. (1997) Measuring Fatigue and Other Anemia-Related Symptoms with the Functional Assessment of Cancer Therapy (FACT) Measurement System. Journal of Pain and Symptom Management; 13:63-74.

13 Appendices



13.3 Appendix 3: Assessment of SpondyloArthritis International Society criteria (ASAS)

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

ASAS domains:

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

[redacted]

13.3.2 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

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

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

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

13.3.3 Appendix 4: Guidelines for administering the PRO questionnaires

1. 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-12 '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.*
2. Patients should have adequate space and time to complete their questionnaires.
3. Questionnaires should be administered and completed before the clinical examination.
4. The administrator may clarify the questions but should not influence the response.
5. Patients should choose one response for each question.

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 an important part of their participation in the study. Patients that refuse to complete PRO questionnaires at Baseline, Week 12 or Week 16 must be discontinued from the study per Section 5.6.2. The goal of these questionnaires is to better understand the physical, mental, and social health problems of patients. Emphasize that this information is as important as any of the other medical information, and that the questionnaire(s) is simple to complete. Suggest that the questionnaire(s) may be different from anything the respondent has filled in the past.

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-reported. 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, that questionnaire will be forfeited since partial response will not be saved. Patients that refuse to complete PRO

questionnaires at Baseline, Week 12 or Week 16 must be discontinued from the study per Section 5.6.2.

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 questionnaires are not routinely shared with treating staff, and that their responses will only be seen by you and possibly the investigator. Any response which may directly impact on or reflect their medical condition (e.g. noting of severe depression) will be communicated by the coordinator to the physician.

General Information about all questionnaire(s):

All questionnaires are to be completed by the patients. 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 verbatim without influencing their answers. The information provided is strictly confidential and will be treated as such.

As there are no source data for the questionnaires, the data queries will be restricted to patient/visit information.