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Global Clinical Development - General Medicine

AIN457/Secukinumab

Clinical Trial Protocol CAIN457F2308 / NCT02896127

A randomized, double-blind, placebo-controlled, phase III multicenter study of subcutaneous secukinumab in prefilled syringes, to compare efficacy at 16 weeks with placebo and to assess safety and tolerability up to 52 weeks in subjects with active Ankylosing Spondylitis

Document type:	Clinical Trial Protocol
EUDRACT number:	2015 - 005021 - 39
Version number:	v01 Clean
Development phase:	III
Release date:	15-Jan-2018

Clinical Trial Protocol Template Version 2.0, November, 2013

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ANCOVA	analysis of covariance
AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis International Society criteria
[redacted]	[redacted]
ASQoL	Ankylosing Spondylitis Quality of Life Questionnaire
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
ATC	Anatomical Therapeutic Classification
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
[redacted]	[redacted]
BSL	Baseline
CFR	Code of Federal Regulation
COX	Cyclooxygenase
(e)CRF	electronic case report form
CRP (hsCRP)	(high sensitivity) C-Reactive Protein
DMARD	Disease Modifying Anti-rheumatic Drug
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
EMA/EMEA	European Medicines (Evaluation) Agency
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
FSH	Follicle-stimulating Hormone
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus

HLA	Human Leukocyte Antigen
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC/EC	Independent Ethics Committee
IFU	Instructions for Use
IL	Interleukin
IN	Investigator Notification
IQS	Integrated Quantitive Sciences
IRB	Institutional Review Board
IRT	Interactive Response Technology
i.v.	intravenous
LLN	lower limit of normal
[redacted]	[redacted]
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Affairs
MMRM	mixed-effects model repeated measures
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NSAID	Non-Steroidal Anti-Inflammatory Drug
OC/RDC	Oracle clinical/remote data capture
PCS	Physical Component Summary
PFS	Prefilled Syringe
PK	Pharmacokinetic
PPD	Purified Protein Derivative
PRO	Patient Reported Outcome
QoL	Quality of Life
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
RDC	Remote Data Capture
SAE	Serious Adverse Event
SCR	Screening
s.c.	Subcutaneous
SF-36	Medical Outcome Short Form (36) Health Survey
SpA	Spondyloarthritis

SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
t.i.d.	ter in die, three times a day
TNF/TNFα	Tumor Necrosis Factor
TNF-IR	TNFα Inhibitor Incomplete Responders
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WBC	White Blood Cell
[redacted]	[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/ time of patient entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)
Epoch / Period	A portion of the study which serves a specific purpose. Typical Epochs are: screening/recruitment, wash-out, treatment, and follow-up
Escape medication	Any new therapeutic intervention or a significant change to ongoing therapy made because a subject is experiencing either no benefit from participation in the trial or worsening/ exacerbation of their disease
Inadequate response to TNFα	Active disease despite stable treatment with anti-TNFα for at least 3 months at a stable dose or for at least one dose in case of lack of tolerance
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CRF 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 definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new treatment." 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 other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
Medication number	A unique identifier on the label of each investigational / study drug package
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 subject, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any treatment administered to the subject as part of the required study procedures; includes investigational treatment and any control drugs
Study/investigational treatment discontinuation	Point/time when subject permanently stops taking study treatment for any reason; may or may not also be the point/time of premature subject withdrawal
Subject number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Amendment 1

Amendment rationale

This protocol amendment is issued for the following reason:

Due to changes in the regulatory environment in China, a primary endpoint analysis can be implemented and used for submission purpose. This will allow a much earlier (approximately 9 months) submission than originally planned. To enable this, an additional analysis will be performed after all patients have completed the Week 16 for the primary endpoint assessments. Although unblinding will occur after the Week 16 database lock, the original randomization to active treatment vs placebo will continue to remain blinded to all investigators, site personnel and patients until all patients have completed the study (Week 60 Follow up) and the final database lock has occurred.

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

Changes to the protocol

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

The wording of the following sections “Purpose and timing of interim analyses / design adaptations” (Section 3.5), “Treatment blinding” (Section 5.4), and “Interim Analysis” (Section 9.6) have been amended to reflect the rationale given above for the primary endpoint analysis.

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

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

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

The changes herein do NOT affect the trial specific model ICF.

Protocol summary

Protocol number	CAIN457F2308
Title	A randomized, double-blind, placebo-controlled, phase III multicenter study of subcutaneous secukinumab in prefilled syringes, to compare efficacy at 16 weeks with placebo and to assess safety and tolerability up to 52 weeks in subjects with active Ankylosing Spondylitis
Brief title	Study of efficacy and safety of secukinumab in patients with Ankylosing Spondylitis
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug; Biologic
Study type	Interventional
Purpose and rationale	To demonstrate the clinical efficacy, safety and tolerability of secukinumab compared to placebo in patients with Ankylosing Spondylitis
Primary Objective(s)	To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 16 is superior to placebo in subjects with active AS based on the proportion of subjects achieving an ASAS20 (Assessment of SpondyloArthritis International Society criteria) response.
Secondary Objectives	To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 16 is superior to placebo based on the proportion of subjects achieving an ASAS40 response To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 16 is superior to placebo based on the change from baseline of high sensitivity C-Reactive Protein (hsCRP) To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 16 is superior to placebo based on the proportion of subjects meeting the ASAS 5/6 response criteria To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 16 is superior to placebo based on the change from baseline in total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 16 is superior to placebo based on the change from baseline in Short Form 36 physical component score (SF-36 PCS) To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 16 is superior to placebo based on the change from baseline in Ankylosing Spondylitis Quality of Life score (ASQoL) To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 16 is superior to placebo based on the proportion of subjects achieving an ASAS partial remission Overall safety and tolerability of secukinumab compared to placebo as assessed by vital signs, clinical laboratory values and adverse event monitoring
Study design	This is a randomized, double-blind, placebo-controlled study

Population	The study population will consist of 450 male and female patients (≥18 years) with moderate to severe AS who fulfill the modified New York criteria for ankylosing spondylitis with prior documented radiological evidence (x-ray or radiologist's report). Patients must have a history of active AS and report active disease, as measured by the following three assessments: - total BASDAI ≥ 4 on a scale of 0-10 - spinal pain as measured by BASDAI question #2 ≥ 4 cm (0-10cm) - total back pain as measured by VAS ≥ 40 mm (0-100 mm) Approximately 80% of randomized patients will be from China (360 Chinese patients) in order to evaluate the efficacy and safety in this patient population.
Inclusion criteria	Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must give written, signed and dated informed consent before any study assessment is performed Male or non-pregnant, non-lactating female patients at least 18 years of age 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 Active AS assessed by BASDAI ≥4 (0-10) **at Baseline** Spinal pain as measured by BASDAI question #2 ≥ 4 cm (0-10 cm) **at Baseline** Total back pain as measured by VAS ≥ 40 mm (0-100 mm) **at Baseline** Patients should have had inadequate response or failure to respond to at least 2 NSAIDs at an approved dose for a minimum of 4 weeks in total and a minimum of 2 weeks for each NSAID prior to randomization, or less than 4 weeks if therapy had to be withdrawn due to intolerance, toxicity or contraindications 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 randomisation Patients who have been on a TNFα inhibitor (not more than one) must have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months prior to randomization or have been intolerant to at least one administration of an anti-TNFα agent Patients who have previously been on a TNFα inhibitor will be allowed to entry into study after an appropriate wash-out period prior to randomization: - 4 weeks for Enbrel® or "Yi Sai Pu"® (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 (s.c. route) - 10 weeks for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route) - 10 weeks for Simponi® (golimumab) – with a terminal half-life of 11-14 days

	- 10 weeks for Cimzia® (certolizumab) – with a terminal half-life of 14 days Patients taking MTX (≤ 25 mg/week) or sulfasalazine (≤ 3 g/day) are allowed to continue their medication, must have taken it for at least 3 months and have to be on a stable dose for at least 4 weeks prior to randomization Patients on MTX must be on stable folic acid supplementation before randomization Patients who are on a DMARD other than MTX or sulfasalazine must discontinue the DMARD 4 weeks prior to randomization, except for leflunomide, which has to be discontinued for 8 weeks prior to randomization unless a cholestyramine washout has been performed Patients taking systemic corticosteroids have to be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization
Exclusion criteria	Chest x-ray or MRI with evidence of ongoing infectious or malignant process obtained within 3 months of screening and evaluated by a qualified physician Patients with total ankylosis of the spine Patients taking high potency opioid analgesics (*e.g.* methadone, hydromorphone, morphine) Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor Use of any investigational drug and/or devices within 4 weeks of randomization or a period of 5 half-lives of the investigational drug, whichever is longer History of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes Any therapy by intra-articular injections (*e.g.* corticosteroid) within 4 weeks before randomization Any intramuscular corticosteroid injection within 2 weeks before randomization Patients previously treated with any biological immunomodulating agents except for those targeting TNFα Patients who have taken more than one anti-TNFα agent Previous treatment with any cell-depleting therapies, including but not limited to anti-CD20, investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19) Traditional Chinese medicine treatment for AS four weeks before randomization 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 hCG laboratory test Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the entire study or longer if required by locally approved prescribing information (e.g., 20 weeks in EU). Active ongoing inflammatory diseases other than AS that might confound the evaluation of the benefits of secukinumab therapy, including inflammatory bowel disease or uveitis

	Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromised the patient and/or places the patient at unacceptable risk in case of use of immunomodulatory therapy Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV), uncontrolled diabetes or very poor functional status precluding ability to perform self-care History of clinically significant liver disease or liver injury indicated by abnormal liver function tests, such as SGOT (AST), SGPT (ALT), alkaline phosphatase and serum bilirubin. History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.5 mg/dl (132.6 µmol/L) Screening total WBC count <3,000/µl, or platelets <100,000/µl or neutrophils <1,500/µl or hemoglobin <8.5 g/dl (85 g/L) Active systemic infections during the last two weeks (exception: common cold) prior to randomization 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 or a positive QuantiFERON TB-Gold test Known infection with HIV, hepatitis B or hepatitis C at screening or randomization History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, in situ carcinoma of the cervix or non-invasive malignant colon polyps that have been removed) Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins) 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 Blood donation or loss of 400 mL or more blood within 8 weeks before dosing History or evidence of ongoing alcohol or drug abuse within the last six months before randomization Plans for administration of live vaccines during the study period or 6 weeks prior to randomization
Investigational and reference therapy	Secukinumab 150 mg s.c. Matching placebo
Efficacy assessments	Assessment of SpondyloArthritis International Society (ASAS) response criteria Patient's global assessment of disease activity (on VAS scale)

	Patient's assessment of back pain intensity (on VAS scale) Bath Ankylosing Spondylitis Functional Index (BASFI) Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [redacted] hsCRP [redacted]
Safety assessments	QuantiFERON TB-Gold test or PPD skin test Chest X-ray or MRI Physical examination Vital signs Height and weight Laboratory evaluations [redacted] Electrocardiogram Pregnancy and assessment of fertility Local tolerability (Injection site reactions) Tolerability of secukinumab
Other assessments	Health-related Quality of Life SF-36 ASQoL [redacted] HLA-B27 [redacted]
Data analysis	The statistical hypothesis for ASAS20 being tested is that there is no difference in the proportion of subjects fulfilling the ASAS20 criteria at Week 16 in the secukinumab 150 mg regimen versus placebo regimen.
Key words	Ankylosing spondylitis, AS, chronic inflammatory disease, inflammatory back pain, secukinumab, AIN457

1 Introduction

1.1 Background

Ankylosing spondylitis (AS) is a chronic inflammatory disease which belongs to a group of conditions known as spondyloarthritides. It is mainly characterized by involvement of the axial skeleton and the sacroiliac joints, but also affects peripheral joints, entheses and extra-articular organs. A significant proportion of patients may present with associated extra-articular manifestations such as uveitis, psoriasis, inflammatory bowel disease, 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 antigen is strongly associated with AS: 90–95% of patients with AS who have European or Chinese ancestry carry this marker. Prevalence of HLA-B27 varies with ethnicity and is approximately 8% among the general population in China (Huang 2012).

AS affects up to 1.1% of the population, is associated with significant morbidity and disability, and thus constitutes a major socioeconomic burden. The prevalence of AS in China has been reported to range from 0.2% to 0.54% and is similar to that seen in other parts of the world (Bao 2014).

The first-line drug treatment of mild AS consists of non-steroidal anti-inflammatory drugs (NSAIDs). Treatment of NSAIDs-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. Tumor necrosis factor (TNF) blocking agents were successfully added to the armamentarium to treat AS (Braun 2002) and subsequently demonstrated prolonged efficacy during 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 only be suppressed but not completely abolished. Results reported in the ASSERT study, the largest study ever conducted on Magnetic Resonance Imaging (MRI) evaluation of spinal lesions in AS, demonstrated a near complete resolution of inflammatory lesions at the 24 week time point with anti-TNF therapy (Braun 2006). However, in other reports, AS inflammatory bone lesions depicted by MRI did not completely disappear under TNF antagonist therapy over a six-month study period. The bone lesions persisted despite full clinical remission, which suggests that the inflammatory process was still smoldering (Zochling 2007). Structural damage may be significant and is usually irreversible, with both osteoproliferative and osteodestructive changes observed on imaging studies. Multiple modalities are currently used to detect early and late structural changes, such as MRI, conventional x-ray, quantitative computed tomography and dual energy x-ray absorptiometry scan. Classic radiographic findings include syndesmophytes, with progression to total spinal fusion in some cases. Radiographs of the sacroiliac joint often show sclerosis, erosion, and eventually fusion.

Together, these observations indicate that other treatments are needed to treat patients who do not respond to TNF blockers and/or who have incomplete resolution of inflammatory changes as evidenced on MRI studies. Current treatment options for patients with intolerance or an inadequate response to anti-TNFα agents are limited due to slow onset of activity, inconvenient

maintenance i.v. dosing for some regimens, and safety concerns. Interleukin (IL)-17A antagonism by secukinumab represents a novel approach to interfere with the chronic inflammatory process by selectively targeting the predominant cytokine of the unique subset of helper Th17 cells, as well as other cells that play a role in inflammation. Animal data suggest that IL-17 blockade reduces receptor activator of nuclear factor kappa-B ligand (RANKL) dependent osteoclastogenesis upstream of TNF alpha (Koenders 2005). Serum sRANKL levels and sRANKL/ osteoprotegerin ratios are up-regulated in patients with AS and have a relationship with bone mineral density and radiological changes (Kim 2006). Notably, secukinumab showed very good efficacy in subjects with AS based upon results of the Proof of Concept study (CAIN457A2209), in which the ASAS20 (Assessment of Spondyloarthritis International Society criteria) response rate at Week 6 was achieved by approximately 60% of the patients.

Assuming a potential role of Th17 cells in the inflammatory infiltrate in AS, it can be speculated that locally disturbed homeostasis of osteoclastogenic and osteoblastogenic mechanisms characteristic of spondyloarthritis (SpA) might be amenable to correction via IL-17 antagonism.

1.2 Purpose

The purpose of this global study is to provide up to 52 weeks of efficacy, safety and tolerability data to support registration of secukinumab for subcutaneous self-administration in subjects with active AS despite current or previous NSAID, DMARD and/or anti-TNFα therapy. Efficacy and safety data may be used to support the registration of secukinumab in China and other countries with a significant population of Asian ethnicity, for the treatment of active AS.

2 Study objectives

2.1 Primary objective

To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 16 is superior to placebo in subjects with active AS based on the proportion of subjects achieving an ASAS20 (Assessment of SpondyloArthritis International Society criteria) response.

2.2 Secondary objectives

1. To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 16 is superior to placebo based on the proportion of subjects achieving an ASAS40 response
2. To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 16 is superior to placebo based on the change from baseline of high sensitivity C-Reactive Protein (hsCRP)
3. To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 16 is superior to placebo based on the proportion of subjects meeting the ASAS 5/6 response criteria
4. To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 16 is superior to placebo based on the change from baseline in total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

5. To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 16 is superior to placebo based on the change from baseline in Short Form 36 physical component score (SF-36 PCS)
6. To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 16 is superior to placebo based on the change from baseline in Ankylosing Spondylitis Quality of Life score (ASQoL)
7. To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 16 is superior to placebo based on the proportion of subjects achieving an ASAS partial remission
8. Overall safety and tolerability of secukinumab compared to placebo as assessed by vital signs, clinical laboratory values and adverse event monitoring

3 Investigational plan

3.1 Study design

This multicenter study uses a randomized, double-blind, placebo-controlled, parallel-group design. A screening (SCR) period running up to 10 weeks before randomization will be used to assess eligibility, followed by 52 weeks of treatment.

At baseline, patients will be randomized to one of the two treatment groups:

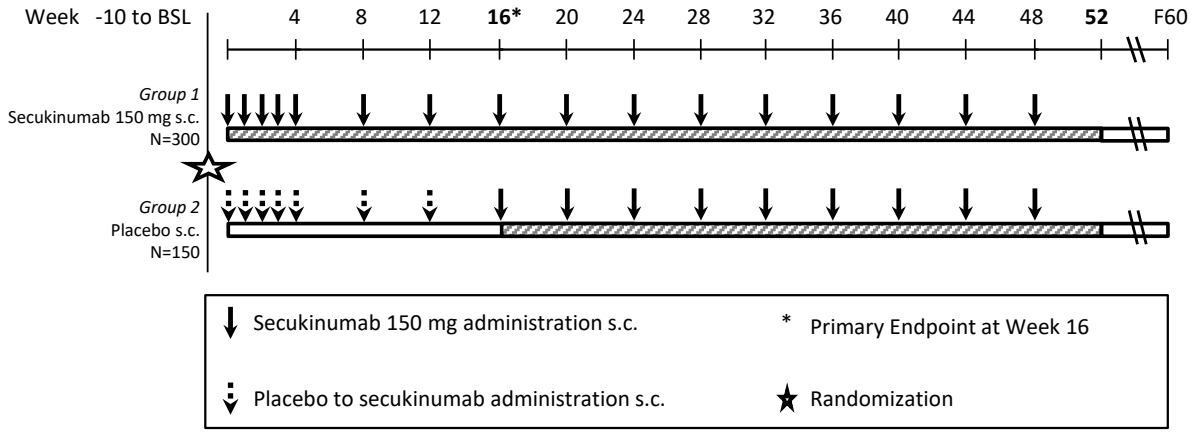
- **Group 1: 300 patients,** secukinumab 150 mg (1 mL, 150 mg/mL) s.c. PFS at BSL, Weeks 1, 2, and 3, followed by administration every four weeks starting at Week 4
- **Group 2: 150 patients,** placebo (1 mL) s.c. PFS at BSL, Weeks 1, 2, 3, 4, 8, and 12, followed by secukinumab 150 mg (1 mL, 150 mg/mL) administration every four weeks starting at Week 16

The patients will be stratified at randomization according to the region (China and non-China). Approximately 80% of randomized patients will be from China (360 Chinese patients) in order to evaluate the efficacy and safety in this patient population. No more than 30% TNFα Inhibitor Incomplete Responders (TNF-IR) patients will be enrolled in the study.

Starting at Week 16, all patients will switch to open-label secukinumab 150 mg, including all placebo patients; however, all patients and investigators/site staff will remain blinded to the original randomized treatment group assignment (150 mg vs placebo). Study treatment will continue up to Week 48.

An end of treatment visit is to be done 4 weeks after last study treatment administration and a post treatment follow-up visit is to be done 12 weeks after last study treatment administration for all subjects (regardless of whether they complete the entire study as planned or discontinue prematurely).

Figure 3-1 Study design



Subjects will be instructed in detail how to self-administer the s.c. injection using PFS. Each injection will be administered into an appropriate injection site of the body (thighs, arms, or abdomen). All injections will be performed at the study site. Site personnel may administer the injections to subjects who are not able to, or feel insecure to self-administer (see Section 5.5.4 for more details).

Rescue medication is not allowed until Week 20 (see Section 5.5.6 for more details). However, subjects who are deemed by the investigator not to be benefiting from the study treatment based on safety and efficacy assessments or for any reason of their own accord will be free to discontinue participation in the study at any time.

3.2 Rationale of study design

The double-blind, randomized, parallel-group, placebo-controlled design used in this global study is aligned with Phase III trials of other biologics and is in accordance with EMA/EMEA (European Medical Agency) guidelines (EMEA 2009) and available precedent. The treatment duration of the placebo group was kept relatively short and the group will be re-assigned to active treatment at the end of the primary endpoint analysis. The blinding to original treatment assignment is maintained beyond the primary endpoint so as to ensure reliable efficacy and safety measures over time, although study treatment from Week 16 on will be open-label secukinumab 150 mg s.c., as all patients will be on this same dose for the remainder of the study through Week 48. The regular assessments of disease activity ensure that subjects who experience worsening of the disease in any of the treatment groups can exit the study upon their own wish or based on the advice of the investigator at any time.

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

The dosing regimens in this study rely on dose-efficacy relationships observed in the following AS studies:

- A proof of concept trial (CAIN457A2209)
- Phase III trial CAIN457F2310 in AS

- Phase III trial CAIN457F2305 in AS

Dose selection:

The AS trials CAIN457F2305 and CAIN457F2310 assessed the efficacy of both 75 mg and 150 mg s.c. maintenance doses with loading regimens consisting of either intravenous (CAIN457F2305: 3 doses of 10 mg/kg given every 2 weeks at Weeks 0, 2, and 4) or subcutaneous doses (CAIN457F2310: 4 weekly doses matching the maintenance dose of either 75 mg or 150 mg given at Weeks 0, 1, 2, and 3). The relative exposure of the i.v. loading regimen (e.g., 700 mg x 3 doses = 2100 mg total through Week 4 for an average 70 kg adult patient) was higher than the s.c. loading regimens of 75 mg and 150 mg (75 or 150 mg x 5 doses = 375 or 750 mg total, respectively, through Week 4) and, theoretically, would exceed the drug exposure obtainable with a 300 mg s.c. loading regimen (300 mg x 5 doses = 1500 mg total through Week 4). Although neither CAIN457F2305 nor CAIN457F2310 assessed a 300 mg dose, the observation that the higher exposure from the i.v. loading regimen in CAIN457F2305 did not provide greater efficacy than the 150 mg s.c. loading regimen in CAIN457F2310 suggests that doses higher than 150 mg would not provide an additional efficacy benefit in AS.

Specifically, the ASAS20, ASAS40, and BASDAI responses seen at the Week 16 primary endpoint for the 150 mg dose in each of these studies, regardless of whether the loading dosing was i.v. (CAIN457F2305) or s.c. (CAIN457F2310; 60.8% for i.v.-150 mg vs 28.7% for placebo; 61.1% for 150 mg s.c. vs 28.4% for placebo for ASAS20, respectively), demonstrate that 150 mg is sufficient to provide clinically and statistically significant efficacy, whereas higher doses of secukinumab do not confer additional benefit. Of note, the 75 mg s.c. loading/s.c. maintenance regimen tested in CAIN457F2310 did not achieve statistically significant improvements in any of the efficacy endpoints in a predefined testing hierarchy, including ASAS20, ASAS40, hsCRP, ASAS5/6, BASDAI, SF-36-PCS, ASQoL and ASAS partial remission. Therefore, the 75 mg dose will not be pursued in further studies.

Subcutaneous administration in PFS:

Subcutaneous administration of secukinumab would extend the treatment options available to subjects with AS, particularly those wishing to self-administer their therapy. Subcutaneous administration of secukinumab has been studied in multiple phase II (psoriasis and RA) and phase III trials (uveitis, psoriasis, psoriatic arthritis, AS and RA) at doses ranging from 25, 75, 150, to 300 mg every 4 weeks. In all these studies, subcutaneous administration of secukinumab was well tolerated and did not demonstrate clinically meaningful levels of immunogenicity.

Subcutaneous injection from prefilled syringes (PFS) will provide a better treatment experience and added convenience compared with a lyophilisate requiring reconstitution or intravenous dosing. Patients with chronic diseases who are able to self-inject their medication demonstrate greater control of their treatment schedule and treatment setting, thus allowing greater independence, better adherence, improved therapeutic outcomes and freedom in their social, domestic, and professional lives, which results in economic benefits to both the patient and the healthcare system (Kivitz 2006; Chilton 2008). Self-injection may also offer psychological benefits over administration by healthcare professionals, including improved self-esteem (Hamm 2000).

Bioequivalence between the secukinumab lyophilisate and PFS formulations have been established in study CAIN457A2106 in 150 healthy volunteers in which the pharmacokinetics, safety and tolerability of the PFS and the lyophilisate formulation were compared. The ratio of PK exposure point estimates and confidence intervals for the two formulations were within the 0.8-1.25 boundaries and therefore, the PFS met the standard criteria for assuming bioequivalence. The use of the PFS was safe and well tolerated. Therefore, it is considered appropriate to use secukinumab in PFS in multiple pivotal phase III studies, including this study, in the same dose and regimen as in the phase III studies that used the lyophilisate formulation. In summary, initial administration with four weekly doses of secukinumab 150 mg s.c. followed by maintenance dosing every 4 weeks at the same s.c. dose in PFS is expected to provide a rapid onset of action and statistically significant treatment effect.

3.4 Rationale for choice of comparator

A placebo arm up to the primary endpoint at 16 weeks is included in this study. Due to the nature of the disease and the outcome measures used (ASAS criteria), a placebo arm is necessary to obtain reliable efficacy measurements. The continuation of the placebo group can be supported from an ethical standpoint, as subjects can continue on a range of concomitant treatments. Moreover, the inclusion of a placebo group is in accordance with health authority guidelines including EMA and available precedent.

3.5 Purpose and timing of interim analyses/design adaptations

Analyses may be done after all patients complete the Week 16 visit of the study and before the final end-of-study analysis to support health authority review. The final analysis will be conducted after all patients complete the study at Week F60.

Although unblinding will occur after the Week 16 database lock, the original randomization to active treatment vs. placebo will remain blinded to all investigators, site personnel and patients until all patients have completed the study and the Week F60 database lock has occurred.

3.6 Risks and benefits

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

As of Jul-2015, over 12000 subjects have been enrolled in both completed and ongoing studies with secukinumab, with over 9600 patients across various indications (plaque psoriasis, rheumatoid arthritis, AS, psoriatic arthritis, multiple sclerosis, uveitis, Crohn's disease, dry eye, polymyalgia rheumatica) and healthy subjects having received secukinumab 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.

The risk profile of secukinumab in AS is informed by the safety experience from arthritides and psoriasis trials. In the dose-ranging rheumatoid arthritis trial CAIN457F2201 (237 patients), the most common side effects were infections in about 20-30% of patients (most mild to moderate). Gastrointestinal disorders were experienced by 8-12% of patients, skin rashes by 7-10%, joint

and muscle aches by 5-8%, and headaches by 1-3% of patients. However, these side effects were also seen in patients who received placebo.

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

Taking into account the available safety data for the individual risks outlined in the IB, the expected risk profile of secukinumab from a mechanism of action perspective is anticipated to be similar compared with other approved cytokine-targeting therapies. In some trials, infections were numerically higher in the secukinumab treatment groups than in the placebo cohorts, although no dose-dependent increase in rates of serious infections was observed. This indicates that there may not be a direct exposure related effect on host defense. The safety data from the completed studies do not suggest any unexpected safety risk of concern or any particular pattern of event clustering other than those outlined in the IB. From the standpoint of the overall risk benefit assessment, the current trial with secukinumab is justified.

4 Population

The study population will be comprised of patients (≥18 years old at the time of consent) with moderate to severe AS who fulfill the modified New York criteria for ankylosing spondylitis (described in Appendix 3) with prior documented radiological evidence (x-ray or radiologist's report).

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

- total BASDAI ≥ 4 on a scale of 0-10
- spinal pain as measured by BASDAI question #2 ≥ 4 cm (0-10cm)
- total back pain as measured by visual analog scale (VAS) ≥ 40 mm (0-100 mm)

This is a global study and it is expected that approximately 450 subjects will be randomized. Approximately 80% of randomized patients will be from China (360 Chinese patients) in order to evaluate the efficacy and safety in this patient population. A screening failure rate of 30% and post-randomization drop-out rate of 10% at primary endpoint are anticipated. Enrollment will stop as soon as the target number of randomized subjects is reached. No more than 30% TNF-IR patients will be enrolled in the study.

Patients can be re-screened only once and no study-related re-screening procedure should be performed prior to written re-consent by the subject. Mis-randomization occurs when a subject who does not meet all eligibility criteria receives a randomization number in IRT in error; mis-randomized patients will be treated as screen failures and will not be re-screened.

4.1 Inclusion criteria

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

1. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must give 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 (Appendix 3),
4. Active AS assessed by BASDAI ≥4 (0-10) **at Baseline**
5. Spinal pain as measured by BASDAI question #2 ≥ 4 cm (0-10 cm) **at Baseline**
6. Total back pain as measured by VAS ≥ 40 mm (0-100 mm) **at Baseline**
7. Patients should have had inadequate response or failure to respond to at least 2 NSAIDs at an approved dose for a minimum of 4 weeks in total and a minimum of 2 weeks for each NSAID prior to randomization, or less than 4 weeks if therapy had to be withdrawn due to 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 randomisation
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 randomization or have been intolerant to at least one administration of an anti-TNFα agent
10. Patients who have previously been on a TNFα inhibitor will be allowed to entry into study after an appropriate wash-out period prior to randomization:
    a. 4 weeks for Enbrel® or "Yi Sai Pu"® (etanercept) – with a terminal half-life of 102 ± 30 hours (s.c. route)
    b. 8 weeks for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (s.c. route)
    c. 10 weeks for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route)
    d. 10 weeks for Simponi® (golimumab) – with a terminal half-life of 11-14 days
    e. 10 weeks for Cimzia® (certolizumab) – with a terminal half-life of 14 days
11. Patients taking MTX (≤ 25 mg/week) or sulfasalazine (≤ 3 g/day) are allowed to continue their medication, must have taken it for at least 3 months and have to be on a stable dose for at least 4 weeks prior to randomization
12. Patients on MTX must be on stable folic acid supplementation before randomization
13. Patients who are on a DMARD other than MTX or sulfasalazine must discontinue the DMARD 4 weeks prior to randomization, except for leflunomide, which has to be

discontinued for 8 weeks prior to randomization unless a cholestyramine washout has been performed

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 randomization

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study.

1. Chest x-ray or MRI with evidence of ongoing infectious or malignant process obtained within 3 months of screening and evaluated by a qualified physician
2. Patients with total ankylosis of the spine
3. Patients taking high potency opioid analgesics (e.g. methadone, hydromorphone, morphine)
4. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor
5. Use of any investigational drug and/or devices within 4 weeks of randomization or a period of 5 half-lives of the investigational drug, whichever is longer
6. History of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes
7. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization
8. Any intramuscular corticosteroid injection within 2 weeks before randomization
9. Patients previously treated with any biological immunomodulating agents except for those targeting TNFα
10. Patients who have taken more than one anti-TNFα agent
11. Previous treatment with any cell-depleting therapies, including but not limited to anti-CD20, investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)
12. Traditional Chinese medicine treatment for AS four weeks before randomization
13. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the entire study or longer if required by locally approved prescribing information (e.g., 20 weeks in EU). Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the 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) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female 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). For UK: with spermicidal foam/gel/film/cream/ vaginal suppository
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
- Placement of an intrauterine device or intrauterine system

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

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

15. Active ongoing inflammatory diseases other than AS that might confound the evaluation of the benefits of secukinumab therapy, including inflammatory bowel disease or uveitis
16. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromised the patient and/or places the patient at unacceptable risk in case of use of immunomodulatory therapy
17. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV), uncontrolled diabetes or very poor functional status precluding ability to perform self-care
18. History of clinically significant liver disease or liver injury indicated by abnormal liver function tests, such as SGOT (AST), SGPT (ALT), alkaline phosphatase and serum bilirubin. The investigator should be guided by the following criteria:
    - Any single parameter may not exceed 2 x the upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out laboratory error.
    - If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into direct and indirect reacting bilirubin.

19. History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.5 mg/dl (132.6 µmol/L)
20. Screening total WBC count <3,000/µl, or platelets <100,000/µl or neutrophils <1,500/µl or hemoglobin <8.5 g/dl (85 g/L)
21. Active systemic infections during the last two weeks (exception: common cold) prior to randomization
22. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5 mm or according to local practice/guidelines) or a positive QuantiFERON TB-Gold test as indicated in the assessment schedule in Table 6-1. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment according to local country guidelines must have been initiated
23. Known infection with HIV, hepatitis B or hepatitis C at screening or randomization
24. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, in situ carcinoma of the cervix or non-invasive malignant colon polyps that have been removed)
25. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial
26. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)
27. 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
28. Blood donation or loss of 400 mL or more blood within 8 weeks before dosing
29. History or evidence of ongoing alcohol or drug abuse within the last six months before randomization
30. Plans for administration of live vaccines during the study period or 6 weeks prior to randomization

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Novartis will supply the following study treatments:

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

Subjects will be provided with detailed instructions and guidance on how to self-administer the s.c injection using the PFS and following the Instructions for Use (IFU). The investigational drug will be administered by the subject into the appropriate injection site of the body under the supervision of the site staff. Site staff will administer the injection to subjects who are not able or feel insecure to self-administer the PFS injection.

Note: The prefilled syringes are packed in double-blinded fashion for the blinded portion of the study and do not need to be prepared by the study site.

The study medication will be labeled as follows:

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

5.1.2 Additional study treatment

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

5.2 Treatment arms

At Baseline eligible subjects will be randomized to one of the following two treatment arms in a 2:1 ratio:

- Group 1: Secukinumab 150 mg
- Group 2: Secukinumab Placebo

All Subjects will receive blinded treatment weekly starting at baseline, Weeks 1, 2, 3 and 4, followed by dosing every four weeks starting at Week 4 until Week 16. At Week 16, Group 1 patients will continue using secukinumab 150 mg and Group 2 patients will start receiving secukinumab 150 mg dosing every four weeks. Treatment will be provided open-label from Week 16 onward, as all patients will be taking 150 mg s.c. every 4 weeks; however, subjects, investigators, and site staff will remain blinded to initial randomized group assignment.

5.3 Treatment assignment, randomization

At baseline, all eligible subjects will be randomized to one of the treatment arms via Interactive Response Technology (IRT). The investigator or his/her delegate will contact the IRT after

confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the subject. The randomization number will not be communicated to any of the site staff.

Starting at Week 16, subjects who have been randomized to placebo at baseline will receive secukinumab 150 mg up to Week 52. Although site personnel and subjects are unblinded to current treatment assignment after Week 16 (as all patients will be on secukinumab 150 mg starting at Week 16), original treatment assignment, as per baseline randomization, will remain blinded to the patient, investigator, and site personnel until after final database lock and analyses.

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

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

5.4 Treatment blinding

This is a double-blind randomized treatment trial. Unblinding will occur after Week 16 database lock to support regulatory submission. However, subjects, investigators, site personnel and persons performing the assessments will remain blinded to original treatment assignment from the time of randomization until the final database lock and analyses are completed, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the following exception: bioanalyst; (2) The identity of the original randomized treatments administered through Week 16 will be concealed up to the final database lock and analyses are completed by the use of study treatments in the form of PFS for s.c. injection, filled with secukinumab or placebo, that are identical in appearance, during the double-blind treatment period.

Other unblinding of treatment dose or original randomized treatment assignment before the final database lock and analyses are completed will only occur in the case of patient emergencies (see Section 5.5.12).

The randomization codes associated with patients from whom [redacted] samples are taken will be disclosed to the bioanalyst who will keep [redacted] results confidential until database lock. The bioanalyst will have access to the randomization list to facilitate analysis of the [redacted] samples (i.e., to avoid the unnecessary analysis of placebo samples). Whenever needed or requested by the clinical team, the bioanalyst will share information from [redacted] measurements before clinical database lock in a blinded fashion [redacted].

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

5.5 Treating the patient

5.5.1 Patient numbering

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

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

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

Subjects may be re-screened once and will receive a new Subject Number after they have been re-consented. Subjects who are mis-randomized cannot be re-screened; mis-randomization occurs when a subject who does not meet all eligibility criteria receives a randomization number in error.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with investigational treatment (150 mg secukinumab vs placebo) in packaging of identical appearance.

The investigational treatment packaging for secukinumab/placebo 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 investigational treatment packages to dispense to the subject by contacting the IRT and obtaining the medication numbers. Immediately before dispensing the package to the subject, investigator staff will detach the outer part of the label from the packaging and affix it to the respective source document (Drug Label Form) for the subject.

5.5.3 Handling of study treatment

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

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

The PFS (150 mg active/placebo) sealed in an outer box must be stored in a access controlled/locked refrigerator between 2°C and 8°C (36°F and 46°F) and protected from light and should not be frozen. 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 investigational treatment in a Drug Accountability Log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all partly used and unused investigational treatment (including placebo), packaging, drug labels, and a copy of the completed Drug Accountability log to Novartis as instructed.

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

5.5.4 Instructions for prescribing and taking study treatment

All study treatment (150 mg secukinumab/placebo) will be self-administered by the subject subcutaneously throughout the study, at the study site, after the study assessments for the visit have been completed. Site staff will administer the injection only to those subjects who feel insecure to self-administer the PFS injection.

Detailed instructions for self-administration of the study treatment will be given in the instructions for use (IFU) provided to each subject. Self-injection will take place under the supervision of a site staff member. At the randomization visit, the subject will be instructed by the site staff, utilizing the IFU on how to self-inject via prefilled syringes. Subjects will be asked to raise questions, if they have any, and then to proceed with self-injection of the study drug.

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

At study visits when pre-dose blood has to be drawn (Table 6-1), the subject will self-inject the study treatment only after blood samples have been taken. All dates and times of injections self-administered by the subject during the study must be recorded in the Dosage Administration Record eCRF. Immediately before dispensing the package to the subject, investigator staff will detach the outer part of the label from the packaging and affix it to that subject's source document (Drug Label Form).

Once the s.c. injection has been completed and the condition of the subject is deemed stable by the investigator or designated healthcare professional, the subject can be discharged

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

any reason to attend a study visit as scheduled or if he/she is unable for any reason to take the study treatment as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

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

Study treatment interruption is only permitted if, in the opinion of the investigator, a 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, study treatment should be interrupted for 12 weeks.

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

5.5.6 Escape medication

Escape medication is defined as any new therapeutic intervention or a significant change to ongoing therapy made because a subject is experiencing either no benefit from participation in the trial or worsening/exacerbation of their disease. Escape medication must not be used before completion of Week 20 assessments. Although no subject will be restricted from receiving necessary escape medications for lack of benefit or worsening of disease, if escape with prohibited biologics (as described in Section 5.5.8) occurs, subjects will be discontinued from the study and enter into the follow-up period after an end of study visit. Efficacy will be assessed in detail at every study visit, and subjects who are deemed not to be benefiting from the study treatment based on safety and efficacy assessments by the investigator or for any reason on their own accord will be free to discontinue participation in the study at any time. Changes in NSAID concomitant therapy are permitted after Week 20 assessments as per investigator's clinical judgment. Please see Section 5.5.7 and Section 5.5.8 for details.

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

5.5.7 Concomitant treatment

The investigator should instruct the subject to notify the study site about any new medications (including over-the-counter drugs, traditional Chinese medicine, calcium and vitamins) administered after the subject was enrolled into the study. All medications (other than study treatment), procedures and significant non-drug therapies (including physical therapy and blood transfusions) must be recorded on the Prior and Concomitant medications or Procedures and Significant Non Drug Therapy eCRF. The reason, name of the drug, procedure or non-drug therapy should be listed.

Guidelines for the use of specific medications are provided below:

Methotrexate

Subjects taking MTX (up to 25 mg/week) must be on a stable dose for at least 4 weeks before randomization and maintained stable until Week 52, except if MTX-related adverse events develop.

Folic acid

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

Leflunomide wash-out with cholestyramine

In case of leflunomide treatment, a drug wash-out of 8 weeks has to be performed. However, another wash-out procedure might be considered. Cholestyramine can be given orally to wash-out the drug at a dose of 8 g t.i.d. Cholestyramine reduced plasma levels of the active leflunomide metabolite by approximately 40% in 24 hours and by 49% to 65% in 48 hours in three healthy volunteers. The administration of cholestyramine is recommended in subjects who require a drug elimination procedure. A subject who has received 8 g t.i.d. for 11 days can be safely randomized 4 weeks after the beginning of the 11-day treatment period.

Systemic corticosteroids

Treatment with systemic corticosteroids is permitted up to a maximum daily dose of 10 mg prednisone equivalent and if the dose was stable within the 2 weeks preceding randomization.

Corticosteroid dose reductions below 10 mg prednisone equivalent are permitted after Week 20, although the corticosteroid dose should not be reduced by more than 1 mg prednisone equivalent every 4 weeks.

Intra-articular corticosteroids are not permitted within the 4 weeks preceding randomization and up to Week 20. After Week 20, no more than 1 joint per 24-week period may be injected. No single injection should exceed 40 mg of triamcinolone (or equivalent) and the total dose of intra-articular corticosteroid may not exceed 80 mg of triamcinolone (or equivalent) during any 52-week period. Injection of intra-articular steroids is not permitted within 8 weeks prior to Week 52.

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

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

Subjects regularly using NSAIDs, low strength opioids, or paracetamol/acetaminophen should be on stable dose for at least 2 weeks before randomization to allow inclusion. They should remain on a stable dose in the study up to Week 20.

Subjects taking NSAIDs, low strength opioids or paracetamol/acetaminophen PRN within the 2 weeks before randomization can continue to do so in the study; however, they have to refrain from any intake during at least 24 hours before a visit with disease activity assessment.

After Week 20 assessments are completed, a change in the NSAIDs, low strength opioids, or paracetamol/acetaminophen treatment regimen is permitted

Any change of the NSAIDs, low strength opioids, or paracetamol/acetaminophen treatment during the trial should be recorded on the appropriate prior and concomitant medication eCRF page.

5.5.8 Prohibited Treatment

Table 5-1 Prohibited treatment

Prohibited treatments	Washout period (before randomization)
Etanercept*	4 weeks
Infliximab*	8 weeks
Adalimumab, golimumab, certolizumab*	10 weeks
Unstable dose of MTX or sulfasalazine	4 weeks
Other DMARD (except MTX or sulfasalazine)	4 weeks
Leflunomide	8 weeks
Leflunomide with Cholestyramine washout	4 weeks
Unstable dose of NSAIDs (COX1 or COX2 inhibitors) (until Week 20)	2 weeks
Systemic corticosteroids > 10 mg prednisone equivalent**	2 weeks
Intra-articular steroids injections (until Week 20)	4 weeks
Any biological immunomodulating agents, except those targeting TNFα*	No prior exposure
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)	No prior exposure
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)
Analgesics other than paracetamol/acetaminophen or low strength opioids PRN	4 weeks
Live vaccinations	6 weeks

* These agents fall under the category of biologic immunomodulators and are prohibited medications. Administration of these agents requires study discontinuation (see Section 5.5.8).

** See details about corticosteroid management in Section 5.5.7.

5.5.9 Discontinuation of study treatment and premature withdrawal

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

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

Patients who discontinue study should undergo an end of treatment visit (Week 52) at 4 weeks after last study treatment and then also return after an additional 8 weeks for a final follow-up visit, corresponding to Week F60 (12 weeks after last study treatment; see Table 6-1). The final follow-up visit should be performed before any new treatment is initiated. Study treatment discontinuation must also be recorded in IRT.

Subjects who are prematurely withdrawn from the study will not be replaced.

5.5.9.1 Discontinuation of study treatment

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

- Withdrawal of informed consent
- Emergence of the following adverse events:
  - Any severe or serious adverse event that is not compatible with administration of study medication, including adverse events that require treatment with an unacceptable concomitant medication
  - Onset of lymphoproliferative disease or any malignancy, except for treated basal cell carcinoma, treated actinic keratoses, treated in situ carcinoma of the cervix or non-invasive malignant colon polyps which are being or have been removed
  - Life-threatening infection
- 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 Appendix 1.)
- Pregnancy
- Use of any biologic immunomodulating agent except secukinumab
- Any protocol deviation that results in a significant risk to the subject's safety

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

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

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

5.5.10 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs when a subject does not want to continue participating in the study any more, that is, the subject does not want any further visits, assessments, or study related contact, and does not allow analysis of already obtained biologic material.

If a subject withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information in the Withdrawal of Consent eCRF. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communication or follow-up.

5.5.11 Loss to follow-up

For subjects who are lost to follow-up (i.e., those subjects 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. A patient should not be considered lost to follow-up until his/her scheduled end of study visit would have occurred.

5.5.12 Emergency breaking of assigned treatment code

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

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

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

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

Study drug must be discontinued after emergency unblinding.

5.5.13 Study completion and post-study treatment

A subject will be considered to have completed the study if he/she received a maximum of 52 weeks of study treatment and upon completion of the scheduled study assessments and procedures up to and including Visit F60.

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

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

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 list all of the assessments and indicate with an "X" when the visits are performed.

Subjects should be seen for all visits on the designated day, or as closely as possible to the originally planned visit schedule.

For visits scheduled through Week 4, the study treatment should not be administered within less than 7 days after the previous administration.

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

Subjects who prematurely discontinue study treatment should return for the end of treatment visit (4 weeks after the last study treatment administration), as well as return for the follow-up visit (F60), 12 weeks after last study treatment administration.

If they refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the reason.

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

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

- If the washout period is ≤ 4 weeks, the investigator should proceed directly to Screening visit 2 on the same day and complete all assessments prior to randomization in the next 4 weeks.

- If the washout period is more than 4 weeks, the subject will be instructed to initiate the necessary washout regimen and return for Screening Visit 2 at 4 weeks prior to randomization.

The rationale is that in all cases, Screening Visit 2 should not happen greater than 4 weeks prior to randomization.

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

Table 6-1 Assessment schedule

	Screening[1]		Treatment period																	PTFU
Week	**SV1 -10 to -4**	**SV2 ≤ -4**	**BSL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52***	**F60***
Obtain Informed consent	X																			
Inclusion / exclusion criteria[2,3]	X	X	X																	
Relevant medical history / current medical conditions[2]	X	X	X																	
Prior medications	X	X	X																	
AS assessment and history of extra-axial involvement[4]	X																			
Demography	X																			
Cardiovascular medical history			X																	
Smoking history			X																	
Physical examination		S	S	S	S	S	S	S	S	S	S	S		S		S			S	S
Height		X																		
Weight		X	X							X		X							X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X		X		X			X	X
PPD skin test[5] or QuantiFERON TB-Gold test		X																		
Hepatitis and HIV screen[6]		S																		
Chest X-ray or MRI[7]		S																		

	Screening[1]		Treatment period																PTFU
Week	**SV1 -10 to -4**	**SV2 ≤ -4**	**BSL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52***	**F60***
Hematology, blood chemistry, urinalysis		X	X	X	X	X	X	X	X	X	X	X		X		X			X	X
Serum pregnancy test		X																		
Urine pregnancy test			X				X		X	X		X		X		X			X	X
ECG			X							X									X	
Randomization via IRT			X																	
On-site administration of s.c. study treatment via PFS			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Concomitant medications / non-drug therapy	X	Update as necessary																		
Adverse events / SAE (including reactions at the injection site)[8]	X	Update as necessary																		
[redacted]																				
Patient's global assessment of disease activity (VAS)			X	X	X	X	X	X	X	X	X	X		X		X			X	X
Patient's assessment of back pain intensity (VAS)			X	X	X	X	X	X	X	X	X	X		X		X			X	X
BASFI			X	X	X	X	X	X	X	X	X	X		X		X			X	X
BASDAI			X	X	X	X	X	X	X	X	X	X		X		X			X	X
[redacted]																				
SF-36			X				X			X		X							X	
[redacted]																				

	Screening[1]		Treatment period																PTFU
Week	**SV1 -10 to -4**	**SV2 ≤ -4**	**BSL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52***	**F60***
ASQoL			X				X			X		X							X	
[redacted]																				
High sensitivity C-reactive protein (hsCRP)		X	X		X		X	X	X	X	X	X		X		X			X	X
HLA-B27			X																	
[redacted]																				
Lipid panel[9]			X				X			X		X							X	
Cardiovascular panel			X							X		X							X	
Treatment period completion form																			X	
Follow-up completion form																				X

S: source documentation,

PTFU: post-treatment follow-up

[1] If the subject's washout period ≤ 4 weeks, Screening visit 1 (SV1) and Screening visit 2 (SV2) can be performed on the same day.

[2] Eligibility and relevant medical history assessments are conducted at SV1, SV2 and BSL. The data for all three visits should be recorded on the corresponding eCRFs available at SV1.

[3] A copy of the x-ray or radiologist's report must be kept in the source documentation.

[4] The following eCRFs are to be completed: AS Disease background eCRF, Modified New York criteria for AS eCRF and History of extra-axial involvement eCRF.

[5] The PPD skin test can be performed at any time during the screening period, but it must be read within 72 hours and before randomization

[6] Hepatitis B and/or hepatitis C and/or HIV serology testing to be performed during screening period only if required as per local medical practice or local regulations prior to initiation of therapy. These assessments will be documented in source records only and will not be entered into the eCRF.

[7] A chest x-ray or MRI is required if it was not performed and evaluated within 3 months prior to screening. The x-ray should be performed after it is certain the subject meets inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation. The x-ray may be replaced by an MRI assessment.

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

[9] Sample must be obtained fasting.

* For all subjects who discontinue or withdraw from the study, the investigator should ensure that the subject completes an end of treatment visit) 4 weeks after last study treatment, and also returns after an additional 8 weeks for a post-treatment follow-up (PTFU) visit, F60 (12 weeks after last study treatment).

6.1 Information to be collected on screening failures

Subjects may discontinue from the study prior to randomization. These subjects are considered screening failures.

If a subject discontinues before entering the double-blind treatment period at baseline, IRT must be notified within 2 days and the reason for not being randomized will be entered on the Screening Phase Disposition eCRF page. In addition, only the following eCRFs should be completed: Demography eCRF, Informed Consent eCRF, Inclusion/Exclusion eCRF, AS Disease background eCRF, Modified New York criteria for AS eCRF, History of extra-axial involvement eCRF, and the Adverse event (AE) eCRF should be completed for any Serious Adverse Events (SAEs) that occurred during the screening period. Adverse events that are not SAEs will be followed by the Investigator and collected only in the source data.

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

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

6.2 Patient demographics/other baseline characteristics

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

- Date of birth, age, sex, race, ethnicity and source of subject referral
- Relevant AS and general medical history/current medical condition data until the start of study treatment, history of extra-axial involvement (uveitis, psoriasis, inflammatory bowel disease, dactylitis, enthesitis, peripheral arthritis), number and type of previous DMARDs used, date of diagnosis of AS, previous AS therapies, functional status class according to the New York criteria, cardiovascular medical history and smoking history

Whenever possible, diagnoses and not symptoms will be recorded.

6.3 Treatment exposure and compliance

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

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

Compliance is expected to be 100%, unless temporary interruption is needed for safety reasons as described in (Section 5.5.5).

6.4 Efficacy

- Assessment of SpondyloArthritis International Society (ASAS) response criteria

- Patient's global assessment of disease activity (VAS)
- Patient's assessment of back pain intensity (VAS)
- Bath Ankylosing Spondylitis Functional Index (BASFI)
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- [redacted]
- hsCRP [redacted]

6.4.1 Assessment of SpondyloArthritis International Society criteria (ASAS)

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

Main ASAS domains:

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

Additional assessment domains:

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

6.4.1.1 ASAS Response Criteria-20% (ASAS20)

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

6.4.1.2 ASAS Response Criteria-40% (ASAS40)

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

6.4.1.3 ASAS 5/6 improvement criteria

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

6.4.1.4 ASAS partial remission criteria

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

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

The patient's global assessment of disease activity will be performed using a 100 mm VAS ranging from none to very severe in response to the question *"How active was your disease on average during the last week?*".

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

The patient's assessment of back pain will be performed using a 100 mm VAS ranging from no pain to unbearable pain in response to the question "*Based on your assessment, please indicate what strength of back pain at any time did you experience during the last week?*" and *"Based on your assessment, please indicate what strength of back pain at night did you experience during the last week?"*. For ASAS calculation the total back pain will be used.

6.4.4 Bath Ankylosing Spondylitis Functional Index (BASFI)

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

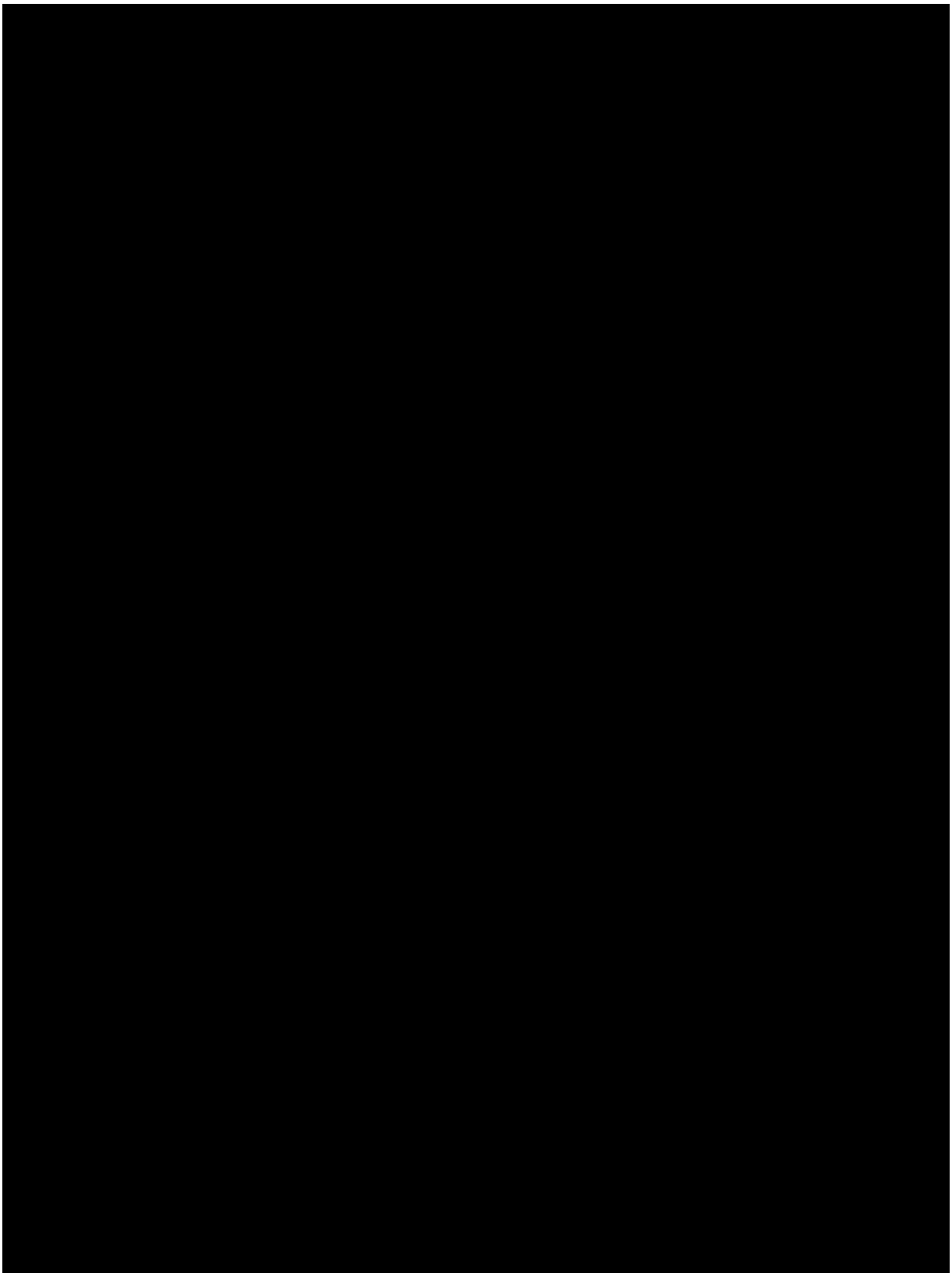
6.4.5 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

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

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

To give each symptom equal weight, the mean (average) of the two scores relating to morning stiffness is taken into account (questions 5 and 6). The resulting 0 to 10 score is added to the scores for questions 1 through 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 the disease and subjects with scores of 4 or greater are usually good candidates for either a change in their medical therapy or enrollment in clinical trials evaluating new drug therapies directed at AS. BASDAI is a quick and simple index taking between 30 seconds and 2 minutes to complete.

[redacted]



[redacted]

6.4.10 High Sensitivity C-reactive protein (hsCRP)

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

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

[redacted]

[redacted]

6.4.13 Appropriateness of efficacy assessments

The efficacy outcome measures used in this study are standard measures used across all AS trials and are required for regulatory filing.

6.5 Safety

- QuantiFERON TB-Gold test or PPD skin test

- Hepatitis and human immunodeficiency virus (HIV) screen
- Physical examination
- Vital signs
- Height and weight
- Electrocardiogram
- Local tolerability (injection site reactions)
- Laboratory evaluations
- Pregnancy and assessment of fertility
- Tolerability of secukinumab
- [redacted]

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

6.5.1 QuantiFERON TB-Gold test or PPD skin test

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

QuantiFERON TB-Gold test

A QuantiFERON TB-Gold test is to be performed at the second screening visit and the results to be known prior to randomization to determine the subject's eligibility for the trial. The test will be used to screen the subject population for latent tuberculosis infection.

The test will be analyzed by the central laboratory. Details on the collection, processing and shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual.

PPD skin test

A PPD skin test is to be performed at screening and read before randomization to determine the patient's eligibility for the trial. The test dose is bioequivalent to 5 tuberculin units of standard PPD injected intradermally, usually into the volar surface of the forearm. The site is cleaned and the PPD extract is then injected into the most superficial layer under the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

Since the reaction (induration) will take 48-72 hours to develop, the patients must return to the investigators' site within that time for a proper evaluation of the injection site. This will determine whether the patient has had a significant reaction to the PPD test. A reaction is measured in millimeters of induration (hard swelling) at the site. A PPD skin induration ≥5 mm (or according to local practice/guidelines) is interpreted as a positive result.

6.5.2 Hepatitis and human immunodeficiency virus (HIV) screen

Screening for hepatitis and HIV is optional, based on the judgment of the investigator or if required by local regulations. If hepatitis testing is performed, testing will include hepatitis B surface antigen (HBsAg) and anti-HCV antibodies. If HIV testing is performed, positive HIV screening will be confirmed by a second technique available at the respective local laboratory, e.g., Western blot.

6.5.3 Chest x-ray or MRI

A chest x-ray or MRI at screening (or within 3 months prior to screening) is performed to rule out the presence of a pulmonary malignancy or infectious process, in particular, tuberculosis.

6.5.4 Physical examination

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

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present before signing the ICF must be included in the relevant medical history eCRF. Significant findings made after signing the ICF that meet the definition of an AE must be recorded in the Adverse Event eCRF.

6.5.5 Vital signs

This will include blood pressure and pulse rate measurements after 5 minutes rest in sitting position.

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

6.5.6 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing) (both without shoes) will be measured.

If possible, body weight assessments should be performed by the same study site staff member using the same scale throughout the study.

6.5.7 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. Single 12 lead ECGs are collected. The original ECGs (on non-heat-sensitive paper or a certified copy on non-heat sensitive paper), appropriately signed, must be collected and archived at the study site.

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

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

6.5.8 Local tolerability (Injection site reactions)

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

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

6.5.9 Laboratory evaluations

A central laboratory will be used for analysis of the specimens collected listed below, with the exception of urinalysis. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual. For the identification of clinically notable values, see Appendix 1. All subjects with laboratory tests with clinically significant abnormal results are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

6.5.9.1 Hematology

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

6.5.9.2 Clinical chemistry

Serum chemistries will include glucose, urea, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorus, total protein, albumin, and uric acid.

6.5.9.3 Lipid panel

A lipid profile including High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), cholesterol and triglycerides will be done from a fasting blood sample.

6.5.9.4 Cardiovascular panel

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

6.5.9.5 Urinalysis

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

6.5.10 Pregnancy and assessments of fertility

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

6.5.11 Tolerability of secukinumab

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

[redacted]

6.5.13 Appropriateness of safety measurements

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

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

6.6 Other assessments

- Quality of Life questionnaires/ Patient reported outcomes (PROs)

[redacted]

- HLA-B27

[redacted]

6.6.1 Quality of Life questionnaires/ Patient reported outcomes (PROs)

The impact of AS on various aspects of subject's health-related quality of life (HRQoL) will be assessed by the following instruments:

- SF-36 v2 (Acute form)
- ASQoL
- [redacted]

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

All questionnaires will be completed at the scheduled study visit prior to the subject seeing the investigator for any clinical assessment or evaluation. The subject should be given sufficient instruction, space, time and privacy to complete the questionnaire. The study coordinator should check the questionnaire for completeness and encourage the subject to complete any missing responses. Guidelines for administering the PRO questionnaires can be found in Appendix 6. A detailed training manual relating to the administrative procedures of the questionnaires will be provided to the sites.

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses that may indicate potential adverse events (AEs) or serious adverse events (SAEs). The investigator should review not only the responses to the questions in the questionnaires, but also any unsolicited comments written by the subject. If AEs or SAEs are confirmed, then the physician must record the events. Investigators should not encourage the subjects to change the responses reported in the completed questionnaires.

The language in which each of the questionnaires to be completed will also be captured the first time a questionnaire is administered.

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

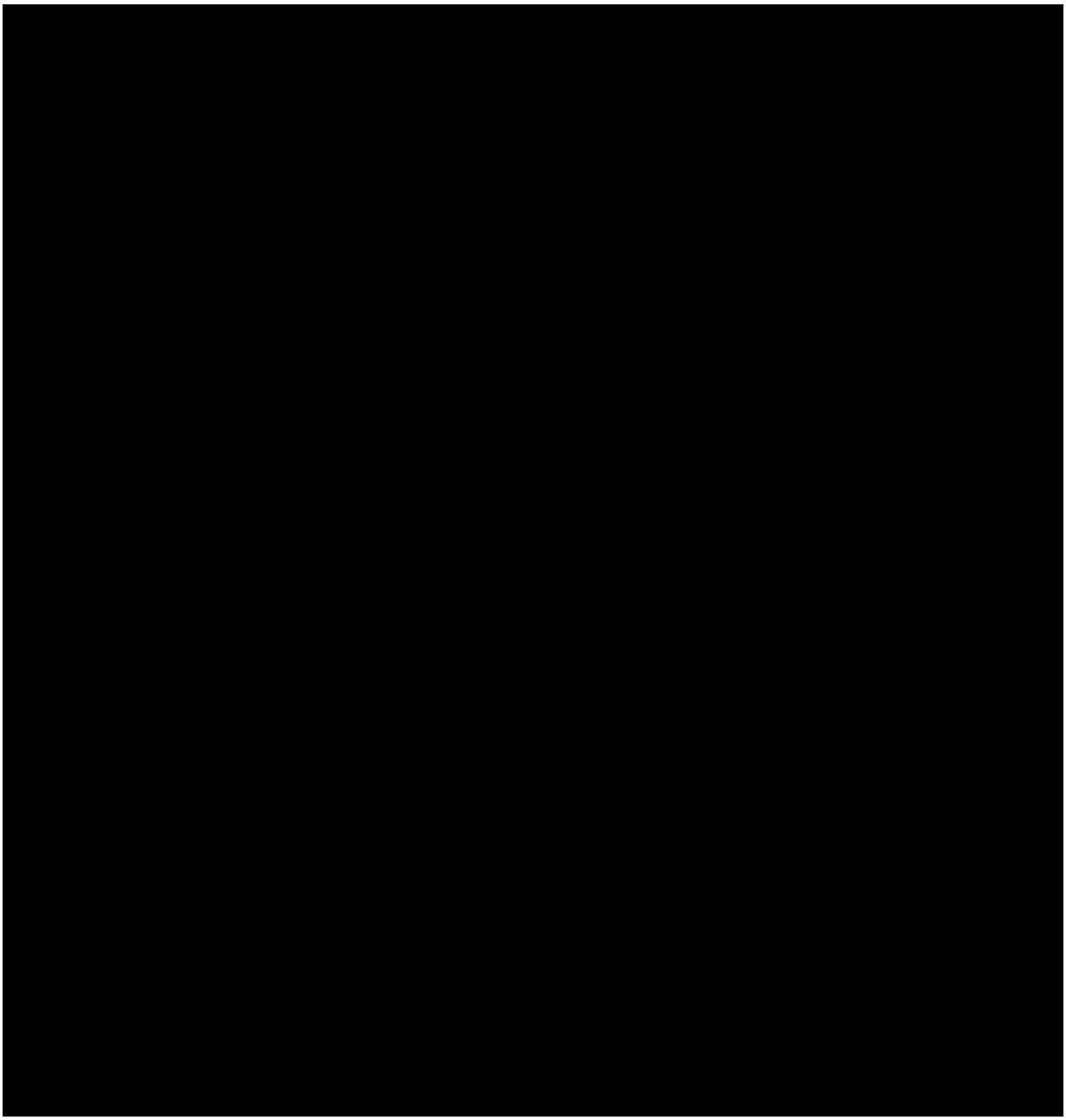
The SF-36 is a widely used and extensively studied instrument to measure health-related quality of life among healthy patients and patients with acute and chronic conditions. It consists of eight subscales that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health (Ware and Sherbourne 1992). Two overall summary scores, the Physical Component Summary and the Mental Component Summary also can be computed (McHorney et al 1993). The SF-36 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual patients.

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

6.6.1.2 Ankylosing Spondylitis Quality of Life (ASQoL)

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

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



6.6.3 HLA-B27

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

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

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.

The occurrence of AEs should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject 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 a subject with underlying disease. Investigators have the responsibility for managing the safety of individual patients and identifying adverse events. Alert ranges for labs are included in Appendix 1.

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

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

An SAE is 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 any of the following:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

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

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see.

All AE's should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e., further observation only); study treatment dosage adjusted/temporarily interrupted; study drug(s) permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the AE should be recorded on the Adverse Event eCRF.

Once an AE 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 treatment, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the IB or will be communicated between IB updates in the form of Investigator Notifications (IN). 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 subject to report any new AE (beyond the protocol observation period) that the patient, or the subject'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 event

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 12 weeks after last administered dose of study treatment or 30 days after the subject has stopped study participation (whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

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

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

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

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

SAEs (initial and follow-up) that are recorded electronically in the OC/RDC system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis DS&E immediately after investigator signature or 24 hours after entry, whichever occurs first.

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

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

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

7.4 Renal safety monitoring

There has been no safety signal for nephrotoxicity with secukinumab to date in over 9600 patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect on the kidney of blocking IL-17A. Standard renal function tests (blood urea nitrogen, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

7.5 Pregnancy reporting

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

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

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

8 Data review and database management

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 eCRFs with the investigators and their staff. During the study, the Field Monitor will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each subject 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 eCRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for

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

8.2 Data collection

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

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

8.3 Database management and quality control

Novartis staff review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

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

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

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

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

8.4 Data Monitoring Committee

A Data Monitoring Committee is neither required nor planned for this study.

8.5 Adjudication Committee

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

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

9 Data analysis

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

Inferential efficacy comparisons with placebo will be performed on the first 16 weeks of treatment.

Data analyses will be presented by treatment regimen. Efficacy and safety data for the placebo-controlled period (or the entire treatment period as appropriate) will be presented by the following 2 treatment groups. Subjects may be included in more than one treatment group for some analyses (e.g. exposure-adjusted adverse events over the entire treatment period). These treatment groups represent the regimens to which subjects will be eligible to be randomized:

Secukinumab 150 mg regimen

Placebo regimen

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

9.1 Analysis sets

The following analysis sets will be used in this trial:

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

Misrandomized subjects are defined as those subjects who were mistakenly randomized in IRT prior to the site confirming all eligibility criteria were met and to whom no study medication was given. Misrandomized patients are treated as screen failures.

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

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

9.2 Patient demographics and other baseline characteristics

Demographics and baseline characteristics

The following common background and demographic variables will be summarized:

- Gender, age, China / non-China, race, ethnicity, weight, height, and BMI

Baseline disease characteristics will also be summarized for the following variables:

- Patient's global assessment of disease activity and other ASAS components, hsCRP, [redacted] prior use of TNF-alpha inhibitors, use (yes/no), and separate dose of MTX (mg/week), sulfasalazine (g/day) and systemic corticosteroids (mg/day) at randomization, time since first diagnosis of AS (years), modified New York criteria for AS, HLA-B27, [redacted] total back pain (VAS), [redacted] total BASDAI score, spinal pain (BASDAI question #2) [redacted].

Medical history

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

To establish a baseline level of cardiovascular risk, the number and percentage of subjects with pre-solicited cardiovascular risk factors will be summarized by treatment group. The number of cardiovascular risk factors that each subject has will also be summarized by treatment group. If it is unknown whether or not a subject currently or previously experienced a specific cardiovascular risk factor, it will be assumed that cardiovascular risk factor did not exist for that subject.

9.3 Treatments

9.3.1 Study treatment

The analysis of study treatment data will be based on the safety set. The number of active and placebo injections received will be presented by treatment group.

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

9.3.2 Prior and concomitant medication

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

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

Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of subjects receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

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

The number and percentage of subjects receiving prior and concomitant ankylosing spondylitis therapy will be presented by randomized treatment group as well as the reasons for stopping their therapies (primary lack of efficacy, secondary lack of efficacy, lack of tolerability, other).

Prior or concomitant medication will be identified by comparing recorded or imputed start and end dates of medication taken to the reference start date.

9.4 Analysis of the primary variable

Details of the testing strategy including primary and secondary endpoints are provided in Section 9.5.1

9.4.1 Variable(s)

The primary efficacy variable is response to treatment according to the ASAS20 criteria at Week 16. The analysis of the primary variable will be based on the FAS.

9.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypothesis for ASAS20 being tested is that there is no difference in the proportion of subjects fulfilling the ASAS20 criteria at Week 16 in the secukinumab 150 mg regimen versus placebo regimen.

Let p_0 denote the proportion of ASAS20 responders at Week 16 for Placebo regimen and p_1 denote the proportion of ASAS20 responders at Week 16 for Secukinumab 150 mg regimen

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

H_1: Secukinumab 150 mg regimen is not different to placebo regimen with respect to ASAS20 response at Week 16

The primary analysis will be conducted via logistic regression with treatment, randomization stratum (region) as factors and weight as a covariate. Odds ratios and 95% CI will be presented comparing secukinumab 150 mg regimen to placebo.

9.4.3 Handling of missing values/censoring/discontinuations

Missing data for ASAS20/40 response and other binary efficacy variables (e.g. ASAS5/6, etc.) will be handled as follows:

1. Subjects who drop out of the trial for any reason will be considered non-responders from the time they drop out through week 16
2. Subjects who do not have the required data to compute response (e.g. ASAS components) at baseline and at the specific time will be classified as non-responders.

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

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

variable, i.e. it might be that the number of subjects providing data to an analysis is smaller than the number of subjects in the FAS.
Data collected after Week 16 will be analyzed as observed cases, in general.

9.4.4 Supportive analyses

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

In order to determine the robustness of the logistic regression model used for the primary analysis, ASAS20 response at Week 16 will also be evaluated using a non-parametric ANCOVA model (Koch 1998) with the same independent variables as the logistic regression model. In addition, further logistic regression models may be conducted which explore the impact of other baseline or disease characteristics on response.

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

- Multiple imputation
- Observed data analysis

9.5 Analysis of other variables

9.5.1 Secondary efficacy variables

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

9.5.1.1 ASAS40 response at Week 16

ASAS40 response at Week 16 will be evaluated using logistic regression with treatment, randomization stratum (region) as factors and weight as a covariate.

9.5.1.2 Change from baseline of hsCRP at Week 16

For the change in hsCRP, since evidence from the literature suggests that the data are not normally distributed (Huffman 2006), analysis will be performed on the $\log_e$ ratio of the treatment value vs. baseline value (calculated by dividing the post-baseline value by the baseline value and then applying the $\log_e$ transformation) to normalize the distribution of hsCRP at each analysis visit. Between-treatment differences in the change in hsCRP relative to baseline will be evaluated using MMRM, with treatment group, analysis visit, randomization stratum (region) as factors, and $\log_e$ baseline hsCRP and weight as continuous covariates. Treatment by analysis visit and $\log_e$ baseline hsCRP by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. The significance of the secukinumab treatment effect for secukinumab regimen at different analysis visits will be determined from the comparisons performed between secukinumab regimen and placebo at the appropriate analysis visits. The estimate and the 2-sided 95% confidence intervals obtained from the model will be back-transformed to the original scale.

9.5.1.3 ASAS 5/6 response at Week 16

ASAS 5/6 response at Week 16 will be evaluated using logistic regression with treatment, randomization stratum (region) as factors and weight as a covariate.

9.5.1.4 Change from baseline in BASDAI at Week 16

The change from baseline to Week 16 in total BASDAI will be analyzed using MMRM with treatment regimen, randomization stratum (region) and analysis visit as factors and weight and baseline score as continuous covariates. Treatment by analysis visit and baseline by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for this model. The significance of the treatment effects for secukinumab regimens at different analysis visits will be determined from the comparisons performed between secukinumab regimens and placebo and/or secukinumab at the appropriate analysis visits.

9.5.1.5 ASAS partial remission

Response at Week 16 to ASAS partial remission criteria will be evaluated using a logistic regression model with treatment, randomization stratum (region) as factors and weight as a covariate.

9.5.1.6 Change from baseline of SF-36 PCS and ASQoL at Week 16

See Section 9.5.4 Health-related Quality of Life.

9.5.1.7 Testing strategy

The following hypotheses will be tested each at 5% level of significance in pre-specified order as mentioned below using fixed-sequence test such that a family-wise type-I-error of 5% is kept:

Primary objectives:

H1: secukinumab 150 mg regimen is not different to placebo regimen with respect to signs and symptoms (ASAS20 response) at Week 16

Secondary objectives:

H2: secukinumab 150 mg regimen is not different to placebo regimen with respect to signs and symptoms (ASAS40 response) at Week 16

H3: secukinumab 150 mg regimen is not different to placebo regimen with respect to change from baseline in hsCRP at Week 16

H4: secukinumab 150 mg regimen is not different to placebo regimen with respect to ASAS 5/6 response at Week 16

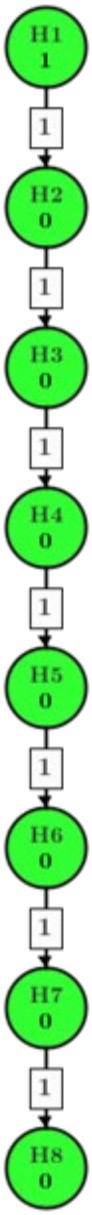
H5: secukinumab 150 mg regimen is not different to placebo regimen with respect to change from baseline in total BASDAI at Week 16

H6: secukinumab 150 mg regimen is not different to placebo regimen with respect to change from baseline in SF-36 PCS at Week 16

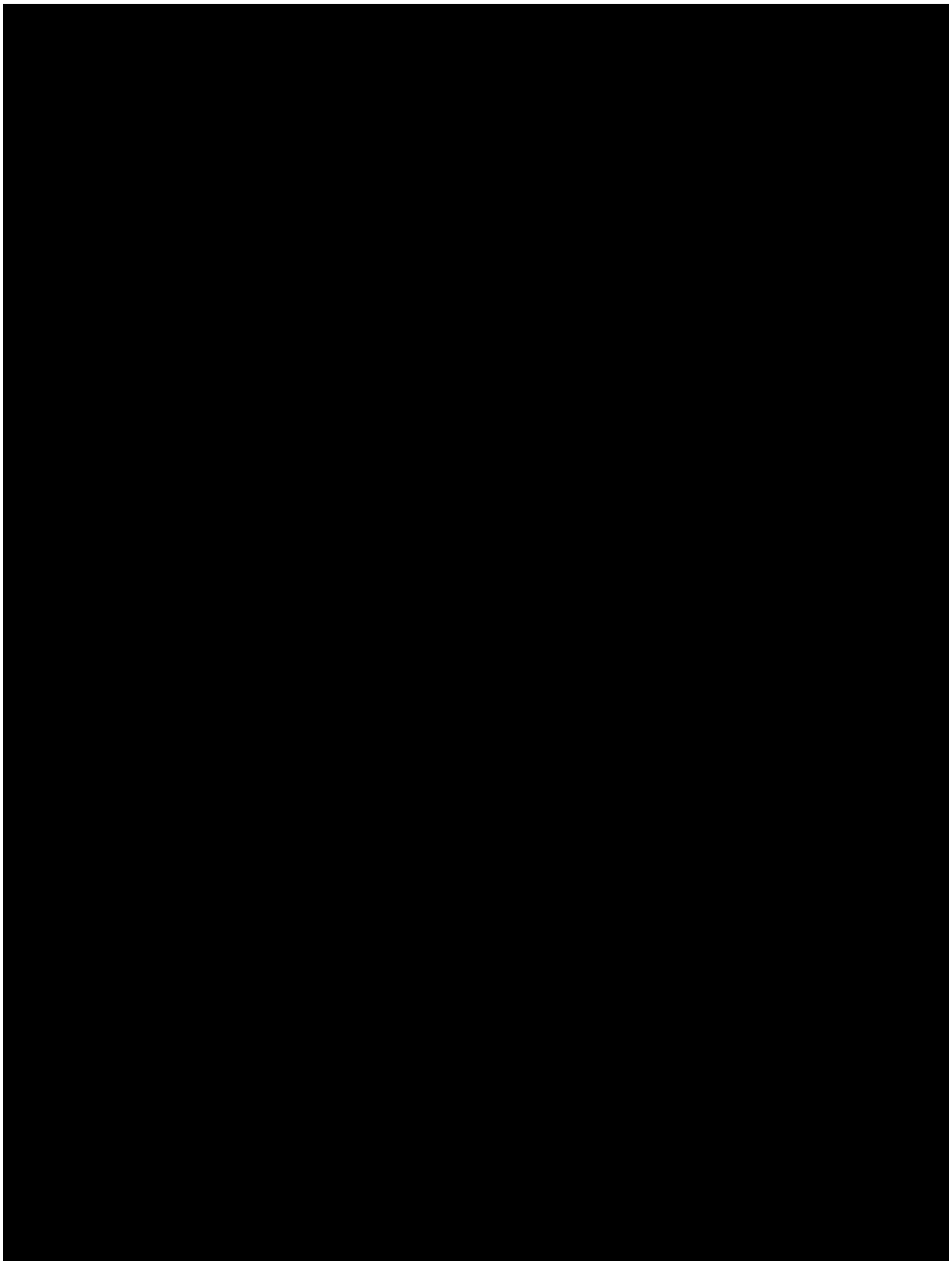
H7: secukinumab 150 mg regimen is not different to placebo regimen with respect to change from baseline in ASQoL at Week 16

H8: secukinumab 150 mg regimen is not different to placebo regimen with respect to ASAS partial remission criteria at Week 16

Figure 9-1 Testing Strategy



The family-wise error will be set to α=5% and it will be controlled with the proposed closed testing procedure.



9.5.3 Safety variables

9.5.3.1 Adverse events

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

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

These summaries may be presented separately by study periods.

As appropriate, the incidence of AEs will be adjusted by treatment exposure and presented per 100 subject-years of exposure.

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

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

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

9.5.3.2 Laboratory data

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

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

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

[redacted]

9.5.3.4 Vital signs

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

9.5.3.5 ECG

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

9.5.4 Health-related Quality of Life

Health-related Quality of Life will be evaluated based on FAS.

9.5.4.1 SF-36

The following variables will be evaluated:

- SF-36 domain scores
- SF-36 PCS and MCS scores
- SF-36 PCS responder (improvement of ≥ 2.5 points; Lubeck 2004)

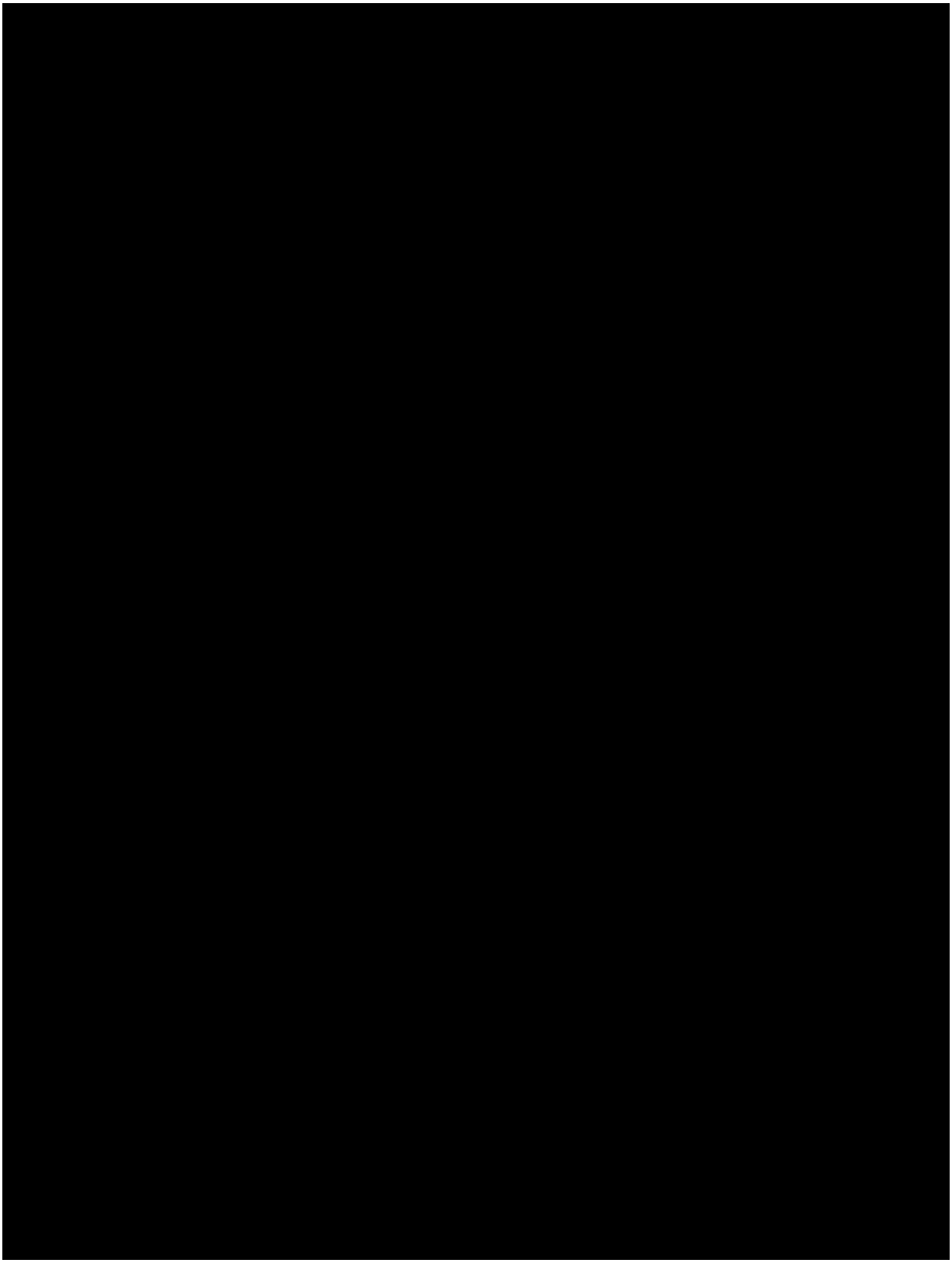
For the change in SF-36 summary scores (PCS and MCS), between-treatment differences will be evaluated using MMRM. Treatment group, analysis visit and randomization stratum (region) will be included as categorical factors and baseline SF-36 score (PCS or MCS) and weight as continuous covariates. Treatment by analysis visit and baseline SF-36 score (PCS or MCS) by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. The significance of the treatment effect for secukinumab regimen at different analysis visits will be determined from the comparisons performed between secukinumab regimen and placebo at the appropriate analysis visits.

In the responder analyses, treatment groups will be compared with respect to response to treatment using a logistic regression model with treatment and randomization stratum (region) as factors, baseline SF-36 PCS score and weight as covariates. Odds ratios and 95% CI will be presented for appropriate treatment comparisons.

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

9.5.4.2 ASQoL

For the change in ASQoL scores, between-treatment differences in the change in ASQoL scores will be evaluated using MMRM. Treatment group, analysis visit, randomization stratum (region) will be used as categorical factors and baseline ASQoL score and weight as continuous covariates. Treatment by analysis visit and baseline ASQoL score by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. The significance of the treatment effect for secukinumab regimen at different analysis visits will be determined from the comparison performed between secukinumab regimens and placebo and/or secukinumab at the appropriate analysis visits.



[redacted]

9.5.6 Pharmacogenetics

Not applicable

9.5.7 Biomarkers

Not applicable

9.6 Interim analyses

The primary endpoint analysis will be performed after all patients complete Week 16 in order to support regulatory submission. As the primary analysis is scheduled at Week 16, no adjustment will be made to the testing strategy to control family-wise type I error rate for this analysis.

9.7 Sample size calculation

The sample size calculation is driven by the patient exposure requirements in the study population. An overall type I error (2-sided) 5% will be used to control type I error. Secukinumab 150 mg regimen will be tested versus placebo with respect to the primary endpoint (ASAS20 response at Week 16). A sample size of 300 patients in secukinumab 150 mg group and 150 patients in placebo group (randomization ratio = 2:1) is chosen in order to expose 300 patients to secukinumab for safety evaluation and also to achieve adequate power for the primary and secondary endpoints for this study.

Analysis of an unpublished phase III study showed a placebo response rate of about 28.4% and active drug response rate of 61.1% after 16 weeks for ASAS20. Using these assumptions, overall, the power for the ASAS20 endpoint should be about 99% with 300 patients in secukinumab 150 mg group and 150 patients in placebo group based on Fisher's exact test (nQuery Advisor 7.0).

9.8 Power for analysis of secondary variables

A summary of the assumptions and power for the primary and secondary efficacy parameters using the same unpublished study is shown in Table 7-1 for binary endpoints and Table 7-2 for continuous endpoints.

Table 7-1 Summary of power for binary endpoints

Endpoint	Response Rate		Power
	Secukinumab 150 mg (N=300)	Placebo (N=150)	
ASAS20	61.1%	28.4%	99%
ASAS40	36.1%	10.8%	99%
ASAS5/6	43.1%	8.1%	99%
ASAS partial remission	13.9%	4.1%	92%

Table 7-2 Summary of power for continuous endpoints

Endpoint	Mean change from baseline		Common standard deviation	Power
	Secukinumab 150 mg (N=300)	Placebo (N=150)		
hsCRP	-0.60	0.12	0.84	99%
Total BASDAI	-2.19	-0.85	2.10	99%
SF-36 PCS	6.06	1.92	6.65	99%
ASQoL	-4.00	-1.37	4.45	99%

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

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

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

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

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.

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.

Anandarajah AP, Schwarz EM, Totterman S, et al. (2008) The effect of etanercept on osteoclast precursor frequency and enhancing bone marrow oedema in patients with psoriatic arthritis. Ann Rheum Dis; 67:296-301.

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; 64:730-734.

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

Biomarkers Definitions Working Group. (2001) Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics; 69:89-95.

Braun J, Brandt J, Listing J, et al. (2002) Treatment of ankylosing spondylitis with infliximab. A randomized controlled multicenter trial. Lancet; 359:1187-93.

Braun J, Landewé R, Hermann K-G, et al. (2006) Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab. Arthritis Rheum; 54:1646-52.

Bretz F, Maurer W, Brannath W, et al. (2009) A graphical approach to sequentially rejective multiple test procedures. Stat Med; 28(4):586-604.

Brown AK, Quinn MA, Karim Z, et al. (2006) Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. Arthritis Rheum; 54:3761-73.

[redacted]

Chilton F, Collett RA. (2008) Treatment choices, preferences and decision-making by patients with rheumatoid arthritis. Musculoskeletal Care.; 6:1–14.

Davis JC, Revicki D, van der Heijde D, et al (2007) Health-related quality of life outcomes in patients with active ankylosing spondylitis treated with adalimumab: results from a randomized controlled study. Arthritis & Rheumatism; 57(6):1050-1057.

[redacted]

EMA guidance document:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2003/09/WC500003439.pdf

[redacted]

Hamm R, Patel B, Whittlestone T, Persad R(2000) Patient self-injection: a new approach to administering luteinizing hormone-releasing hormone analogues. BJU Int; 86:840-842.

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

Huffman K, Samsa G, Slentz C, et al. (2006) Response of high-sensitivity C-reactive protein to exercise training in an at-risk population. Am Heart J; 152(4):793-800.

Inman RD, David JC Jr, et al. (2008) Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum; 58(11):3402-12.

Kim HR, Lee SH, Kim HY, et al. (2006) Elevated serum levels of soluble receptor activator of nuclear factors-kappaB ligand (sRANKL) and reduced bone mineral density in patients with ankylosing spondylitis. Rheumatology; 45(10):1197-200.

Kivitz A, Cohen S, Dowd JE, et al.(2006) Clinical assessment of pain, tolerability, and preference of an autoinjection pen versus a prefilled syringe for patient self-administration of the fully human, monoclonal antibody adalimumab: the TOUCH trial. Clin Ther; 28:1619–1629.

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

Koenders MI, Lubberts E, Oppers Walgreen B, et al. (2005) Blocking of interleukin-17 during reactivation of experimental arthritis prevents joint inflammation and bone erosion by decreasing RANKL and interleukin-1. Am J Pathol; 167:141-9.

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

[redacted]

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

[redacted]

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

van der Heijde D, Dijkmans B, et al. (2005) Efficacy and safety of infliximab in patients with ankylosing spondylitis: Results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum; 52(2):582-591.

van der Heijde D, Kivitz A, Schiff MH, et al. (2006) Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum; 54(7):2136-46.

van Vollenhoven RF, Klareskog L. (2003) Clinical responses to tumor necrosis factor a antagonists do not show a bimodal distribution: Data from the Stockholm Tumor Necrosis Factor a Followup Registry. Arthritis Rheum; 48(6):1500–1503.

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

[redacted]

Zochling J, Baraliakos X, Hermann KG, et al. (2007) Magnetic resonance imaging in ankylosing spondylitis. Curr Opin Rheumatol; 19:346-50.

13 Appendices

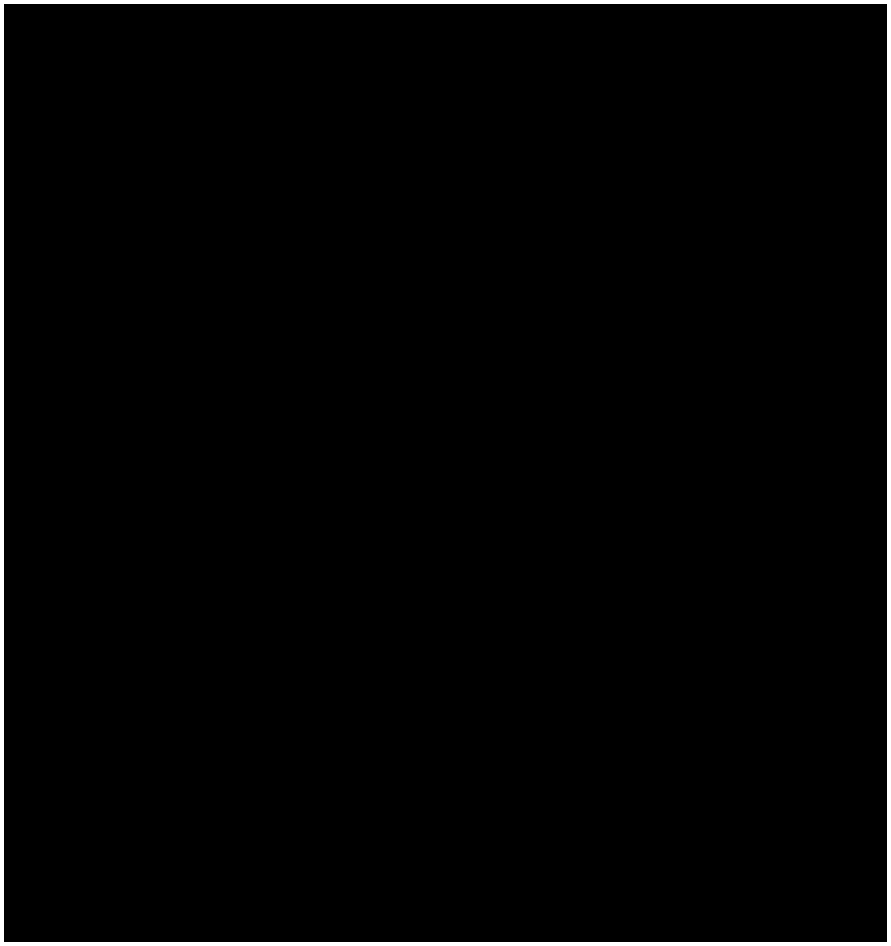
13.1 Appendix 1: Clinically notable laboratory values

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

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

Table 8-1 Safety Analyses: Expanded Limits and Notable Criteria

	Final Harmonization	
Laboratory Variable	**Notable Criteria**	
	Standard Units	**SI Units**
LIVER FUNCTION AND RELATED VARIABLES		
SGOT (AST)	>3 x ULN	>3 x ULN
SGPT (ALT)	>3 x ULN	>3 x ULN
Bilirubin	>2 x ULN	>2 x ULN
Alkaline phosphatase	>2.5 x ULN	>2.5 x ULN
RENAL FUNCTION, METABOLIC AND ELECTROLYTE VARIABLES		
Creatinine (serum)	>2 x ULN	>2 x ULN
HEMATOLOGY VARIABLES		
Hemoglobin	20 g/L decrease from baseline	
Platelet Count	<100x10E9/L	
White blood cell count	<0.8 x LLN	
Neutrophils	<0.9 x LLN	



13.3 Appendix 3: Modified New York criteria

Clinical criteria:

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

Radiological criterion:

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

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

13.4 Appendix 4: Assessment of SpondyloArthritis International Society criteria (ASAS)

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

Main ASAS domains:

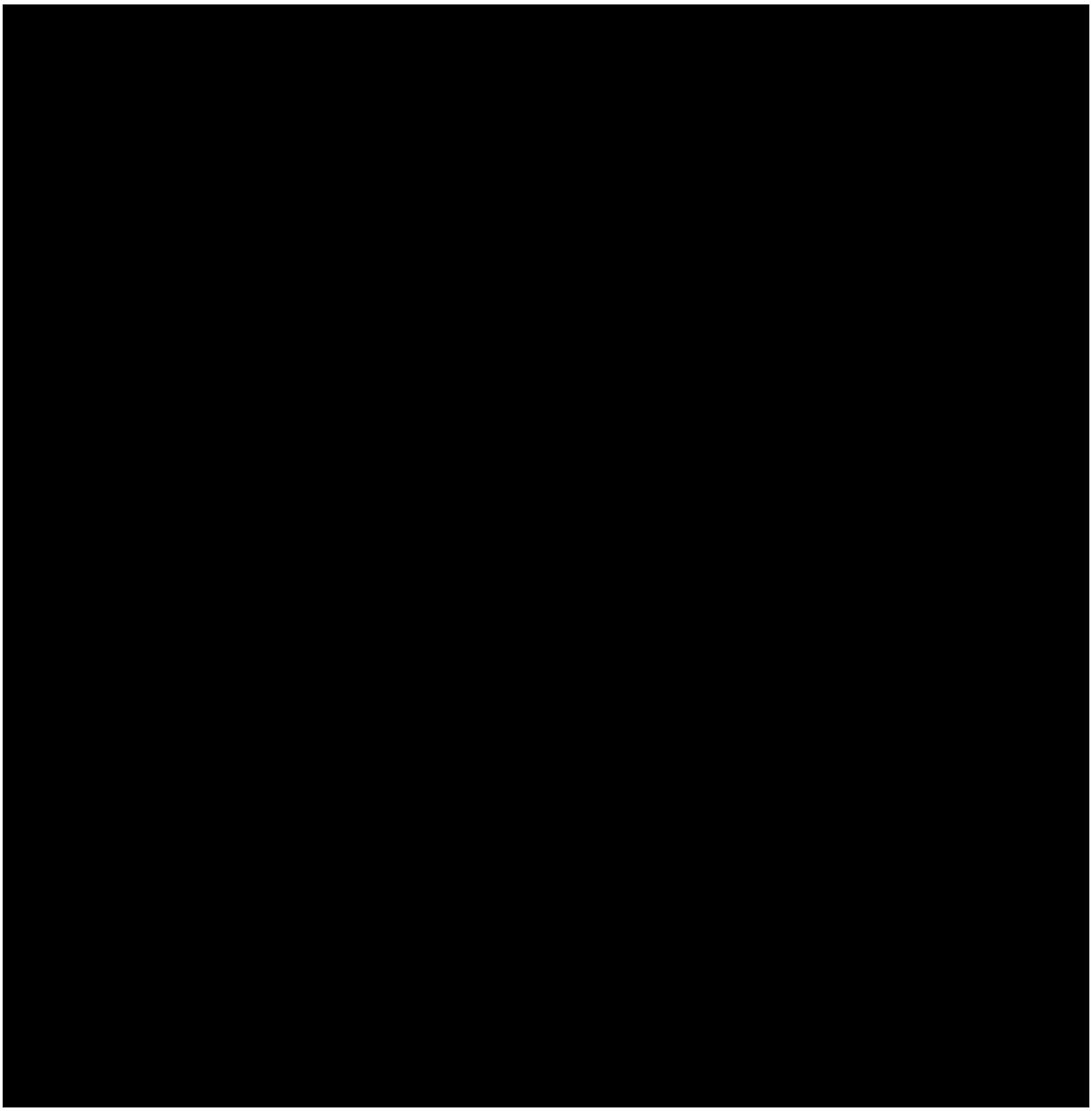
1. Patient's global assessment of disease activity measured on a VAS scale
2. Patient's assessment of back pain, represented by either total or nocturnal pain scores, both measured on a VAS scale
3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured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

Additional assessment domains:

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

13.4.1 Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those subjects with AS. The ten questions were chosen with a major input from subjects with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the subjects' ability to cope with everyday life. A 10cm visual analog scale is used to answer the questions. The mean of the ten scales gives the BASFI score – a value between 0 and 10.



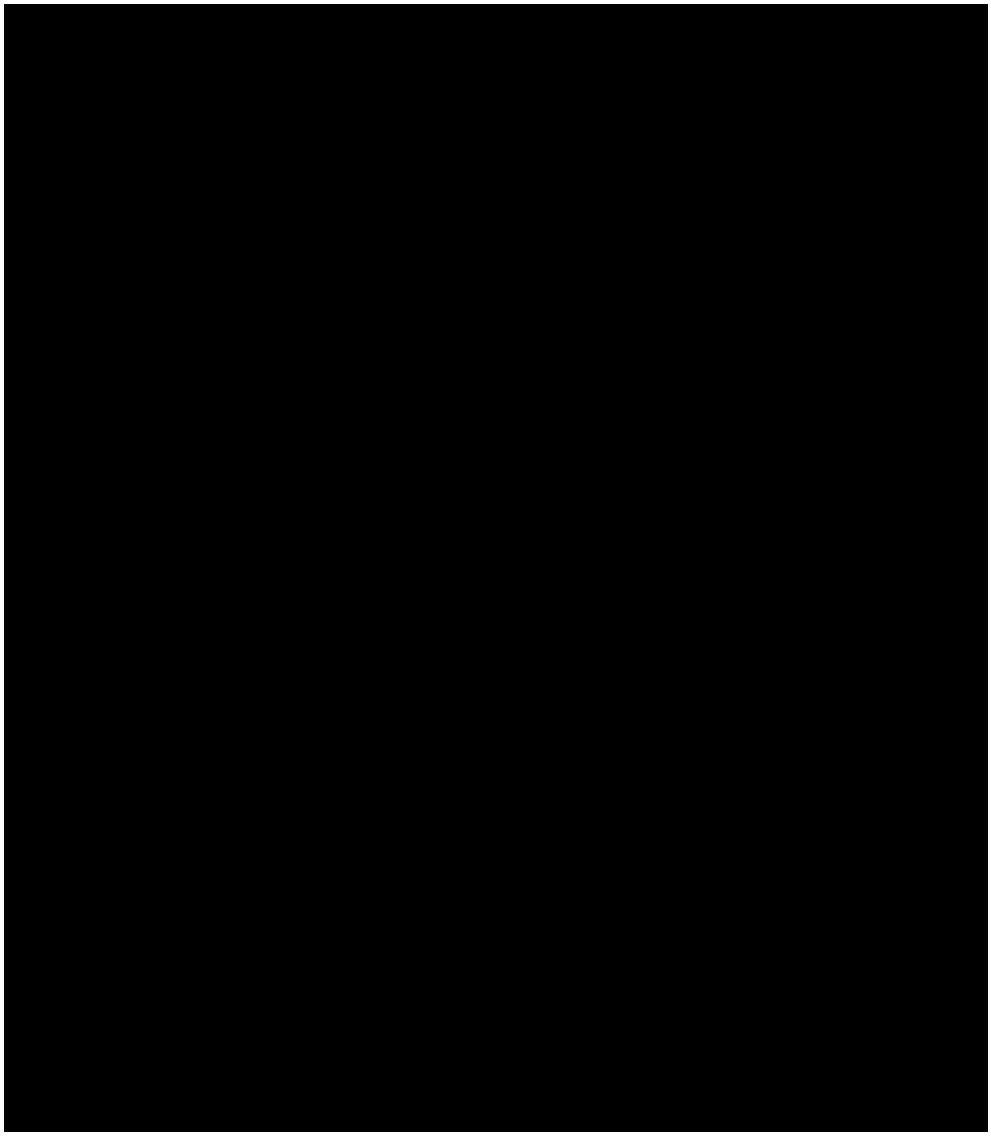
13.4.3 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

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

1. How would you describe the overall level of **fatigue/tiredness** you have experienced?
2. How would you describe the overall level of AS **neck, back or hip pain** you have had?
3. How would you describe the overall level of pain/swelling in joints other than **neck, back, hips** you have had?
4. How would you describe the overall level of **discomfort** you have had from any areas tender to touch or pressure?

5. How would you describe the overall level of **morning stiffness** you have had **from the time you wake up?**
6. How long does your morning stiffness last from the time you wake up?

To give each symptom equal weighting, the mean (average) of the two scores relating to morning stiffness (questions 5 and 6) is taken. The resulting 0 to 10 number 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 trials evaluating new drug therapies directed at Ankylosing Spondylitis. BASDAI is a quick and simple index (taking between 30 seconds and 2 minutes to complete.



13.6 Appendix 6: Guidelines for administering the PRO questionnaires

Before trial begins

Study coordinators should familiarize themselves with the PRO questionnaire(s) in the trial and identify any items where a subject's response might highlight issues of potential concern. *For example, one question in the SF-36 asks 'How much of the time in the past 4 weeks- have you felt downhearted and blue?' If a subject responds 'most or all of the time', then the study coordinator should inform the study investigator.*

Before completion

- Subjects should be provided with the correct questionnaire
  - at the appropriate visits, and
  - in the appropriate language
- Subjects should have adequate space and time to complete the questionnaires
- Questionnaire should be administered before the clinical examination

During completion

- Administrator may clarify the questions but should not influence the response
- Only one response for each question
- Also see 'Addressing Problems and Concerns'

After completion

- Check for completeness and not for content*
- Check for multiple responses that were made in error

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

Addressing Problems and Concerns

Occasionally a subject 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 subject that completion of the questionnaire(s) is voluntary. The goal is to better understand the physical, mental, and social health problems of subjects. 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. If the subject still declines, retrieve the questionnaires. Record the reason for the decline, and thank the subject.

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

In these instances, the coordinator may obtain subject responses by reading out loud each question, followed by the corresponding response categories, and entering the subject's response. No help should be provided to the subject by any person other than the designated study coordinator. The coordinator should not influence subject 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 subject provide responses to the questions. Unless specified in the study protocol proxy data are *not* an acceptable substitute for subject self-report. Subjects 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 subject having trouble understanding particular items, ask the subject to explain the difficulty. Re-read the question for them *verbatim*, but do not rephrase the question. If the respondent is still unable to complete the questionnaire, accept it as incomplete. Thank the subject.

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 subject that his/her answers will be pooled with other subjects' answers and that they will be analyzed as a group rather than as individuals. Tell the subject that completed forms are not routinely shared with treating staff, and that their responses will only be seen by you (to check for completeness), and 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.

The patient asks the meaning of a question/item

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

General information about all questionnaire(s):

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

per question, then this should be brought to patient. Incomplete questions should not be accepted without first encouraging the patient to complete unanswered questions.

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