Global Clinical Development - General Medicine

CAIN457/ Secukinumab

Clinical Trial Protocol CAIN457FDE03 / NCT02763046

A randomized, double-blind, placebo-controlled multicenter study of Secukinumab (AIN457) to examine the clinical efficacy and the NSAID-sparing effect of Secukinumab over 16 weeks in patients with ankylosing spondylitis (ASTRUM)

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AS	Ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis international Society
AST	aspartate aminotransferase
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
b.i.d.	twice a day
BSL	Baseline
CFR	US Code of Federal Regulations
CDS	Core Data Sheet (for marketed drugs)
COX-1 / 2	Cyclooxygenase-1 / 2
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CTRD	Clinical Trial Results Database
DMARD	Disease-modifying antirheumatic drugs
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
ESR	Erythrocyte sedimentation rate
GCP	Good Clinical Practice
hsCRP	High sensitivity C-reactive protein
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions for Use
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology

LFT	Liver function test (raised serum transaminases and/or bilirubin levels)
MedDRA	Medical dictionary for regulatory activities
MTX	Methotrexate
NSAIDs	Nonsteroidal anti-inflammatory drugs
OC/RDC	Oracle Clinical/Remote Data Capture
o.d.	once a day
PFS	Pre-filled syringe
p.o.	per orally
SAE	serious adverse event
s.c.	subcutaneous
SpA	Spondyloarthritides
SUSAR	Suspected Unexpected Serious Adverse Reactions
TNFα	tumor necrosis factor alpha,
VAS	visual analog scale
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication number	A unique identifier on the label of each investigational/study drug package in studies
Period	A subdivision of a cross-over study
Premature subject/patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Amendment 1

Amendment rationale

This protocol amendment is issued for the following reasons:

- Based on results from MEASURE III (CAIN457F2314), MEASURE IV (CAIN457F2320) and COAST V (Ixekizumab - NCT02696785) studies, the assumptions for the power calculation of the primary and a selection of secondary and exploratory objectives were re-evaluated, leading to changes in the statistical analysis plan. The three studies mentioned above suggest that the placebo response might be somewhat higher, leading to a potentially smaller difference between active treatment and placebo than assumed during the planning of this trial. Therefore, in order to keep sufficient power, it was decided to pool the two Secukinumab arms for the primary analysis. This new evaluation triggered an adaption of a set of objectives. The primary objective was adapted so that data of *Group 1* (Secukinumab 150 mg s.c. "delayed tapering") and of *Group 2* (Secukinumab 150 mg s.c. "early tapering") are pooled and ASAS20 response at week 12 are compared against placebo. For the other re-evaluated secondary and exploratoy objectives, data is pooled and is compared against placebo according to the same schema. In the course of this amendment the amount of randomized patients can be reduced to a smaller size (approx. 190) than originally expected (approx. 204), while maintaining adequate power for primary and secondary analyses.
- The amendment is used to describe the ASAS Health Index (chapter 6.4.9) in a more detailed way. Besides the 17 aspects of health, the 9 questions regarding environmental factors in patients with AS are mentioned.

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

1 Introduction

1.1 Background

Ankylosing spondylitis (AS) is a chronic inflammatory disease which belongs to a group of conditions known as spondyloarthritides (SpA). It is mainly characterized by involvement of the axial skeleton and 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. IL-17A has been shown to play an important role in driving the body's immune response in psoriasis and SpA conditions, including PsA and AS (Van Baarsen et al 2011).

Cosentyx® (Secukinumab) is a recombinant monoclonal antibody that neutralizes the activity of IL-17A. Secukinumab is the first IL-17A inhibitor with positive Phase 3 results for the treatment of PsA and AS. In January 2015, Secukinumab (at a dose of 300 mg) became the first IL-17A inhibitor approved in Europe as a first-line systemic treatment for moderate-to-severe plaque psoriasis in adult patients, and in the United States (US) as a treatment for moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy (light therapy). Secukinumab

Clinical trials of Secukinumab in ankylosing spondylitis

The safety and efficacy of Secukinumab has been assessed in 590 patients in 2 randomized, double-blind, placebo-controlled, Phase 3 studies (MEASURE 1: CAIN457F2305; and MEASURE 2: CAIN457F2310, Sieper et al 2015) in patients with active AS with a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 despite non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroid or disease-modifying anti-rheumatic drug (DMARD) therapy. The efficacy and safety of Secukinumab 75 mg and 150 mg were evaluated vs. placebo with either an i.v. or s.c. loading regimen. In the MEASURE 1 and MEASURE 2 study, 27.0% and 38.8% of patients, respectively, were previously treated with an anti-TNFα agent and discontinued the anti-TNFα agent due to either lack of efficacy or intolerance (anti-TNFα-IR patients). The primary endpoint was at least a 20% improvement in Assessment of Spondyloarthritis International Society (ASAS20) criteria at Week 16.

In both AS studies, Secukinumab-treated patients (150 mg in MEASURE 2 and both regimens in MEASURE 1) demonstrated significantly improved signs and symptoms at Week 16; a comparable magnitude of response and efficacy was maintained up to Week 52. The magnitude of response (treatment difference versus placebo) with regards to signs and symptoms at Week 16 was similar in anti-TNFα-naïve and anti-TNFα-inadequate responder patients in both studies, with higher absolute response rates in anti-TNFα-naïve patients. Efficacy was maintained in anti-TNFα-naïve and anti-TNFα-IR patients up to Week 52 in both studies.

In MEASURE 2, treatment with Secukinumab 150 mg resulted in greater improvement in ASAS20, ASAS40, high-sensitivity C-reactive protein (hsCRP), ASAS 5/6 and BASDAI score compared with placebo at Week 16. The onset of action of Secukinumab 150 mg occurred as early as Week 1 for ASAS20 (superior to placebo). ASAS20 responses were improved at Week 16 in both anti-TNFα-naïve patients (68.2% vs. 31.1%; $p<0.05$) and anti-TNFα-IR patients (50.0% vs. 24.1%; $p<0.05$) for Secukinumab 150 mg compared with placebo, respectively.

Non-steroidal anti-inflammatory drugs in ankylosing spondylitis

NSAIDs (including COX-1 or COX-2 inhibitors) are the standard therapy for patients with AS (van der Hejde et al 2011). While effective in relieving pain and improving disease activity in many patients, NSAIDs are associated with side effects that may cause concerns particularly in the context of a life-long treatment at high daily intake doses for diseases such as AS. For example, it has recently been shown that the NSAID diclofenac increases the risk of myocardial infarction in patients with SpA (Dubreuil et al 2014). NSAIDs have also been associated with gastrointestinal side effects (Lanas et al 2006) and a potential acceleration of chronic kidney disease progression (Nderitu et al 2013).

According to the ASAS / European League Against Rheumatism (EULAR) recommendations (van der Hejde et al 2011), patients who show an inadequate response to at least 2 NSAIDs administered at the maximum recommended dose over a total period of 4 weeks should be treated with a biologic. When switching to a biologic in clinical practice, the refractory NSAID treatment is often kept as a concomitant treatment to the biologic. There is currently no clinical or scientific guidance on how, when and how fast NSAIDs should be discontinued or tapered after initiation of the biologic treatment.

Clinical trials have already shown that NSAID intake could be considerably reduced in AS patients treated with anti- TNF compounds (e.g. Poddubnyy et al 2013, Konttinen et al 2007, Braun et al 2002). In these studies, NSAID usage could be reduced in over 50% of patients by more than 50% of the baseline value and could even be completely stopped in up to 20% of the analyzed patients (Braun et al 2002). However, in these trials, patients were not explicitly advised how to reduce NSAIDs. Furthermore, the nonsteroidal anti-inflammatory drug assessment of the spondyloarthritis international society score (ASAS-NSAID score), which has been developed as a standardized method of evaluating NSAID intake in clinical trials has not been used as an endpoint in many of the trials (Dougados et al 2011).

In a recently published prospective, randomized, placebo-controlled trial on the NSAID sparing effect of etanercept (Dougados et al 2014), a dramatic reduction of NSAID intake (up to two thirds) was observed. However, the reduction in NSAID intake was associated with considerably lower clinical ASAS20 response rates compared to the Phase 3 clinical trial of etanercept in AS (i.e. 44% vs. 57% at Week 8). This finding raises questions as to whether or not reducing NSAIDs may potentially counteract the achievement of treatment goals (i.e. reduction of disease activity) and whether or not there is an optimal time point for starting NSAID tapering.

1.2 Purpose

The current study will assess the clinical ASAS20 response to Secukinumab and evaluate to which extent concomitant NSAID treatment can be reduced between Week 4 and Week 12 in patients treated with Secukinumab 150 mg or placebo. Furthermore, the clinical trial will assess the clinical ASAS20 response to Secukinumab and evaluate to which extent concomitant NSAID treatment can be reduced between Week 4 and Week 12 in patients treated with Secukinumab 150 mg or placebo following an initial run-in phase of 4 weeks on stable NSAID therapy. Two different time points of NSAID tapering initiation will be evaluated in this study:

1. a delayed tapering approach in which NSAID will be tapered following 4 weeks of Secukinumab treatment at stable NSAID therapy.

2. an early tapering approach in which NSAID will be tapered immediately after initiation of Secukinumab treatment

These 2 approaches will be evaluated compared to placebo in order to assess whether the early or delayed NSAID tapering is superior to placebo in terms of clinical ASAS20 response and extent of reduction in NSAID intake.

As a patient-reported outcome, pain is a major patient-relevant efficacy parameter in clinical practice in AS. This study will therefore monitor overall neck, back and hip pain on a continuous basis. It will be recommended that NSAID should be tapered if the patient reports an improvement in back pain or a level below a certain threshold. It is anticipated that the results of this study may provide guidance for the systematic adjustment of concomitant NSAID treatment in AS patients based on their initial response to Secukinumab, thereby leading to optimization of the therapeutic strategy with Secukinumab. In case of a positive outcome concerning the NSAID reduction, e.g. no drop in clinical efficacy for Secukinumab between Week 4 and Week 12 at significantly reduced NSAID intake, this study could trigger the development of a guidance concerning NSAID reduction applicable for all AS patients starting a biologic treatment.

2 Study objectives

2.1 Primary objective

To demonstrate that the efficacy of Secukinumab 150 mg s.c. (with NSAID tapering) is superior to placebo based on the proportion of patients achieving an ASAS20 response at week 12. To show superiority, both Secukinumab treatment arms will be pooled and compared against placebo.

2.2 Secondary objectives

1. To demonstrate that the change from baseline in ASAS-NSAID score at week 12 is superior for Secukinumab 150 mg s.c. as compared to placebo. To show superiority, both Secukinumab treatment arms will be pooled and compared against placebo.
2. To demonstrate that the efficacy of Secukinumab 150 mg s.c at week 12 is superior to placebo based on the change from baseline in the total BASDAI. To show superiority, both Secukinumab treatment arms will be pooled and compared against placebo.
3. To demonstrate that the efficacy of Secukinumab 150 mg s.c. (Secukinumab from week 0 with NSAID tapering allowed from week 4; “delayed tapering”) at Week 12 is superior to placebo based on the proportion of patients achieving an ASAS20 response.
4. To demonstrate that the efficacy of Secukinumab 150 mg s.c. (Secukinumab from week 4 with NSAID tapering allowed from week 4; “early tapering”) at Week 12 is superior to placebo based on the proportion of patients achieving an ASAS20 response.
5. To demonstrate that the efficacy of Secukinumab 150 mg s.c. (Secukinumab from week 4 with NSAID tapering allowed from week 4; “early tapering”) at Week 16 is superior to placebo based on the proportion of patients achieving an ASAS20 response.

6. To demonstrate that the change from baseline in ASAS-NSAID score at Week 12 is superior for Secukinumab 150 mg s.c. (Secukinumab from week 0 with NSAID tapering allowed from week 4; “delayed tapering”) as compared to placebo.
7. To demonstrate that the change from baseline in ASAS-NSAID score at Week 12 is superior for Secukinumab 150 mg s.c . (Secukinumab from week 4 with NSAID tapering allowed from week 4; “early tapering”) as compared to placebo.
8. To demonstrate that the efficacy of Secukinumab 150 mg s.c. (Secukinumab from week 0 with NSAID tapering allowed from week 4; “delayed tapering”) at Week 12 is superior to placebo based on the change from baseline in the total BASDAI.
9. To demonstrate that the efficacy of Secukinumab 150 mg s.c. (Secukinumab from week 4 with NSAID tapering allowed from week 4; “early tapering”) at Week 12 is superior to placebo based on the change from baseline in the total BASDAI.
10. To demonstrate that the efficacy of Secukinumab 150 mg s.c. (Secukinumab from week 4 with NSAID tapering allowed from week 4; “early tapering”) at Week 16 is superior to placebo based on the change from baseline in the total BASDAI.
11. To demonstrate that the efficacy of Secukinumab 150 mg s.c. at week 12 is superior to placebo based on the change from baseline in health-related Quality of Life as measured by the SF-36 PCS.
12. To demonstrate that the efficacy of Secukinumab 150 mg s.c. (Secukinumab from week 0 with NSAID tapering allowed from week 4; “delayed tapering”) at Week 12 is superior to placebo based on the change from baseline in health-related Quality of Life as measured by the SF-36 PCS.
13. To demonstrate that the efficacy of Secukinumab 150 mg s.c. (Secukinumab from week 4 with NSAID tapering allowed from week 4; “early tapering”) at Week 12 is superior to placebo based on the change from baseline in health-related Quality of Life as measured by the SF-36 PCS.
14. To compare between both Secukinumab regimens concerning the change from baseline in ASAS-NSAID score after 12 weeks of Secukinumab exposure (ASAS-NSAID index at Week 12 for “delayed tapering” vs. Week 16 for “early tapering”).

2.3 Exploratory objectives

1. To compare between both Secukinumab regimens concerning the change from baseline in the BASDAI after 12 weeks of Secukinumab exposure (BASDAI at Week 12 for “delayed tapering” vs. Week 16 for “early tapering”).
2. To evaluate change in patient reported neck, back and hip pain (BASDAI question 2; Appendix 4) beginning from Secukinumab treatment on a continuous basis in patients exposed to Secukinumab 150 mg s.c. for 12 weeks vs. placebo.
3. To evaluate change in patient reported neck, back and hip pain (BASDAI question 2; Appendix 4) from baseline on a continuous basis in patients randomized Secukinumab 150 mg s.c. (Secukinumab from week 0 with NSAID tapering allowed from week 4; “delayed tapering”) vs. placebo from week 0 to week 12.
4. To evaluate change in patient reported neck, back and hip pain (BASDAI question 2; Appendix 4) from baseline on a continuous basis in patients randomized Secukinumab 150 mg s.c. (early tapering) vs. placebo from week 0 to week 16.

5. To compare ASAS20 response rates at week 4 in Secukinumab 150 mg. s.c. (Secukinumab from week 0 with NSAID tapering allowed from week 4; "delayed tapering") vs. week 20 in the patients switching from Placebo after 4 weeks of Secukinumab exposure each.
6. Total ASAS-NSAID [Area Under Curve (AUC)] Score from treatment start with Secukinumab to a Secukinumab exposure of 12 weeks.
7. Total ASAS-NSAID [Area Under Curve (AUC)] Score from Week 4 to Week 16 for each treatment arm
8. Proportion of patients with no NSAID intake after Secukinumab exposure of 12 weeks
9. Proportion of patients with no NSAID intake at week 12
10. Change from Baseline in the ASAS Health Index after Secukinumab exposure of 12 weeks
11. Change from Baseline in the ASAS Health Index at week 12
12. Spinal mobility assessed by Bath Ankylosing Spondylitis Metrology Index (BASMI) linear scores
13. ASAS40 response rate over time
14. ASAS20 response rate over time
15. ASAS5/6 response rate over time
16. Change from baseline in hsCRP
17. Change from baseline in total BASDAI over time
18. BASDAI 50 response over time
19. ASAS partial remission over time
20. Change from baseline in ASAS components, including:
    a. Patient's global assessment of disease activity
    b. Total spinal pain
    c. Inflammation as measured by the mean of BASDAI questions 5 and 6
    d. Bath Ankylosing Spondylitis Functional Index (BASFI)
21. Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-Reactive Protein (CRP) and ASDAS-Erythrocyte Sedimentation Rate (ESR)
22. ASDAS inactive disease as defined by ASDAS < 1.3
23. ASDAS clinically important improvement (change in ASDAS ≥ 1.1) and major improvement (change in ASDAS ≥ 2.0)
24. To assess overall tolerability and safety of Secukinumab at reduced NSAID intake.
25. To evaluate the reasons given by the patient in the patient diary on why he was not able to taper NSAIDs despite reduced spinal pain
26. To compare both Secukinumab regimens between week 12 (delayed tapering) and week 16 (early tapering) concerning all primary, secondary and exploratory objectives [at these timepoints, patients will have had the same exposure time to Secukinumab of 12 weeks]

3 Investigational plan

3.1 Study design

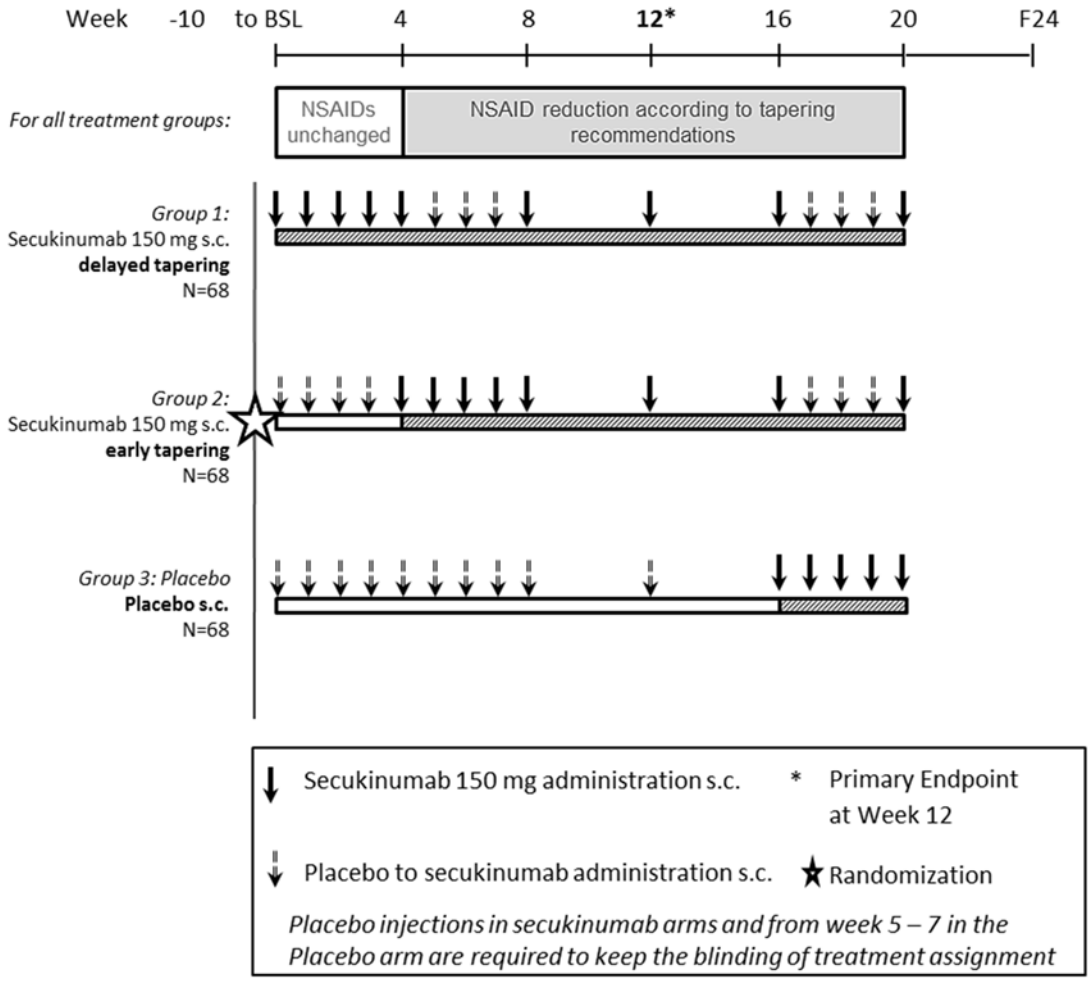
This is a 20-week, randomized, double-blind, 3-arm, placebo-controlled, parallel-group, multicenter study of Secukinumab (AIN457) to examine the clinical response as measured by the ASAS20 and the NSAID-sparing effect of Secukinumab treatment. The clinical efficacy (ASAS20 response) and the cumulative NSAID sparing effect of two strategies of NSAID tapering after initiation of Secukinumab will be evaluated as compared to placebo:

Patients will be randomized 1:1:1 to one of the following treatment groups:

- **Secukinumab - delayed NSAID tapering:** Secukinumab 150 mg s.c. at weeks 0, 1, 2, 3, 4, 8, 12, 16 and 20 with placebo injections at Week 5, 6, 7 and 17, 18, 19 to maintain the blind.
- **Secukinumab – early NSAID tapering:** Placebo at weeks 0, 1, 2, 3 to maintain the blind; followed by Secukinumab 150 mg s.c. at Week 4, 5, 6, 7, 8, 12, 16 and 20 with intermittent Placebo injections at week 17, 18, 19 to maintain the blind.
- **Placebo:** Placebo at weeks 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. After the Week 16 assessments of the secondary endpoint have been performed, these patients will receive Secukinumab 150 mg s.c. at weeks 16, 17, 18, 19 and 20.

The patients will be stratified at randomization according to their status of prior TNFα inhibitor exposure, i.e. TNFα inhibitor naive patients or TNFα inhibitor inadequate responders (TNFα-IR). The only condition that will be placed on enrollment targets for each stratum is that no less than 60% of patients (122 patients) are TNFα inhibitor naïve, i.e., no more than 40% of patients (82 patients) are TNFα-IR. In theory the percentage of TNFα inhibitor naïve patients could reach 100%, although that is not anticipated.

Figure 3-1 Study design



All patients will be advised to continue on the maximum recommended/tolerated dose of NSAIDs for the first 4 weeks of the trial.

A follow-up visit is to be done 4 weeks after last study treatment administration for all subjects, regardless of whether they complete the entire study as planned or discontinue prematurely.

NSAID tapering strategy

All patients will be advised to taper/discontinue their NSAID intake starting at Week 4 to Week 20. Patients may use NSAIDs on an on-demand basis to avoid an unacceptable worsening of disease activity.

From Week 16 on, those patients originally randomized to placebo will self-inject Secukinumab 150 mg at weeks 17, 18, 19 and 20, while patients originally randomized to either of the Secukinumab groups will receive their next Secukinumab injection after Week 16 at Week 20 with Placebo injections at weeks 17, 18, 19 to maintain the blinding of the treatment assignment for the secondary / exploratory endpoint analyses.

Patients will be asked to capture NSAID intake and level of AS neck, back and hip pain (BASDAI question 2; see Appendix 4) on a daily basis in a patient diary. Guidance will be

provided to patients that NSAID intake should be reduced upon an improvement in back pain and that the reduction should preferably happen step-wise and instead of an abrupt stop of any NSAID intake. However, deviance from this guidance will be acceptable and may be discussed between investigator and patient. Patients may deviate from this guidance if required, e.g. NSAID use necessary for non-spinal pain (e.g. entheses, peripheral joints, and headache). Also, if pain levels increase, patients may increase NSAID usage on an on-demand basis. The reduction in NSAID intake will be assessed using the ASAS-NSAID score (Dougados et al 2012).

3.2 Rationale of study design

This phase IV trial utilizes a double-blind, randomized, parallel-group, placebo-controlled design. According to the ASAS/EULAR recommendations (van der Hejde et al. 2011); patients who show an inadequate response to at least 2 NSAIDs over a 4-week period in total at the maximum recommended dose patients should be treated with a biologic unless contraindicated. When switching to a biologic, in clinical practice the refractory NSAID treatment is kept as concomitant treatment in addition to the biologic treatment. There is currently no clinical or scientific guidance on how, when and how fast NSAIDs should be discontinued.

In the current study it will be evaluated to which extent NSAID treatment can be reduced between Week 4 and Week 12 in patients randomized to Secukinumab 150 mg or placebo following an initial run-in phase of 4 weeks on stable NSAID therapy. Two NSAID tapering approaches will be evaluated in this study:

1) an early tapering approach in which NSAID will be tapered at the start of Secukinumab treatment,

2) a delayed tapering approach in which NSAID will be tapered following 4 weeks of Secukinumab treatment.

These 2 strategies will be evaluated compared to placebo in order to assess whether the early or delayed NSAID tapering is superior in terms of clinical ASAS20 response and NSAID sparing strategy.

The ASAS-NSAID score was developed as a standard method of evaluating NSAID intake in clinical studies (Dougados et al 2011; Dougados et al 2012). There, the current study will use the ASAS-NSAID score to assess the potential NSAID sparing effect of Secukinumab.

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

The dosing of Secukinumab in this study with 4-weekly 150 mg s.c injections after weekly Secukinumab 150 mg s.c. loading doses for the first 4 weeks of therapy relies upon dose-efficacy relationships observed in a proof of concept (PoC) trial (CAIN457A2209) and 2 phase III trials (CAIN457F2305, CAIN457F2310) in AS, as described below.

The PoC trial in AS (CAIN457A2209) suggested that after 2 i.v. Secukinumab doses of 10 mg/kg given 3 weeks apart, Secukinumab demonstrated high efficacy, achieving an ASAS20 response at Week 6 in 59% of the patients on Secukinumab versus 24% on placebo, and was well-tolerated (Baeten 2013). The ongoing trials in AS, CAIN457F2305 and CAIN457F2310, assessed the efficacy of both 75 mg and 150 mg s.c. maintenance doses with loading regimens

consisting of either intravenous doses (CAIN457F2305: 3 doses of 10 mg/kg given every 2 weeks at BSL, Weeks 2 and 4) or subcutaneous doses (CAIN457F2310: 4 weekly doses matching the maintenance dose of either 75 mg or 150 mg given at BSL, Weeks 1, 2, and 3). Given the similarity of the ASAS20 response 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: 60.8% for IV-150 mg vs 28.7% for placebo) or s.c. (CAIN457F2310: 61.1% for IV-150 mg vs 27.0% for placebo), 150 mg is a sufficient dose to provide clinically and statistically significant efficacy, whereas higher i.v. loading doses of Secukinumab do not appear to confer a greater response on the primary endpoint of ASAS20 at Week 16. 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 tested in a pre-defined 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.

3.4 Rationale for choice of comparator

The use of early and delayed tapering arms is to evaluate when and how fast NSAIDs can be discontinued after initiating Secukinumab therapy.

A placebo arm up to week 16 is included in this study. Due to the nature of the disease and the outcome measures used (e.g., ASAS20), a placebo arm is necessary to obtain reliable efficacy measurements. This is particularly important as all primary and key secondary endpoints of this trial are based on patient reported outcomes which may be more susceptible to bias in an open label setting. The continuation of the placebo group up to including the week 12 injection can be supported from an ethical standpoint, as patients can continue on a range of concomitant treatments. To obtain unbiased results for the primary endpoint analysis and the blinded evaluation of different time points of initiation of NSAID tapering, it is necessary to switch placebo patients not before all week 16 assessments have been performed and to maintain blinding for the initial treatment group assignment.

Moreover, the inclusion of a placebo group is in accordance with previously implemented methodology and in compliance with the EMA/EMEA (European Medicines Agency) guidelines for clinical trials in AS (EMA 2009).

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

The risk to patients 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).

Data from two pivotal trials in ankylosing spondylitis (AS) CAIN457F2305 and CAIN457F2310 demonstrate safety and efficacy of Secukinumab in the treatment of AS.

Based on these data secukinumab was approved on 19 November 2015 by the European Commission for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

3.6.1.1 Study CAIN457F2305 in ankylosing spondylitis (AS)

This 104-week, double-blind, placebo-controlled study randomized 371 patients with moderate to severe ankylosing spondylitis (AS) despite current or previous NSAIDs, DMARDs and/or TNF-α inhibitor therapy to 10mg/kg IV load (baseline, Week 2, and Week 4)-75 mg sc every 4 wks maintenance (n=124); IV load regimen-150 mg sc maintenance (n=125), or to placebo IV load and sc maintenance (n=122). At Week 16, non-responder placebo pts would be randomized to 75mg or 150mg maintenance dose without a loading regimen and all remaining (responder) placebo pts would be randomized to 75mg or 150 mg maintenance regimen at Week 24. The primary objective was superiority to placebo based on Assessment of Spondyloarthritis International Society criteria (ASAS) 20 response rate at week 16.

An interim analysis with a cut-off date of 10-Dec-2013 was performed and included efficacy data up to Week 52 and all safety data up to that cut-off date of the study for all patients (regardless of study visit at that time). Over the entire treatment period at time of the data cut-off, the median duration of exposure was 475 days for any 75 mg group and 463 days for any 150 mg group.

Both secukinumab arms were superior to placebo for the primary endpoint of ASAS 20 response at Week16: 59.7% for IV-75 mg and 60.8% for IV-150 mg ($p<0.0001$) vs. 28.7% for placebo. Additionally, both secukinumab IV-75 mg and IV-150 mg groups were superior to placebo at Week 16 for all endpoints tested in the hierarchical testing strategy. Among those, ASAS 40 response was 33.1% ($p=0.0003$) for IV-75 mg and 41.6% ($p<0.0001$) for IV-150 mg compared with 13.1% for placebo and significantly lower ratios of post-baseline to baseline hsCRP values for IV-75 (0.45) and IV-150 mg (0.40) vs. placebo (0.97) were reported (both comparisons, $p<0.0001$).

Secukinumab was efficacious through 16 weeks of treatment in both anti-TNF-α naive patients and patients with an inadequate response or intolerance to prior anti-TNF-α therapy. ASAS 20 and ASAS 40 response rates for secukinumab vs. placebo observed for TNF-α inhibitor naive pts were numerically higher (ASAS 20 (60.0% and 66.3%) and ASAS 40 (34.4% and 48.9%)) than for TNF-α inhibitor inadequate responders (ASAS 20: 58.8% and 45.5%; ASAS 40: 29.4% and 21.2%) for the IV-75 mg and IV-150 mg regimens, respectively.

All treatment responses on primary and secondary variables at Week 16 were sustained through Week 52, with dose-separation observed between the IV-150 mg and IV-75 mg regimens as patients approached Week 52, which favored the higher maintenance dose of 150 mg sc on higher hurdle clinical efficacy endpoints such as ASAS 40, ASAS partial remission, and BASDAI 50.

The safety profile of secukinumab for both IV loading regimens showed no new or unexpected safety signals. Infections were more frequent with secukinumab compared to placebo and showed dose dependence in non-serious infections, with the majority consisting of upper respiratory tract infections. Serious infections were rare in both secukinumab treatment arms.

Two deaths were reported: a suicide secondary to depression in a placebo patient, and respiratory failure secondary to cardiac failure and pulmonary fibrosis in a patient on IV-75 mg. Neither death was suspected to be related to study treatment.

The incidence of AEs up to Week 16 was higher in both IV-75 mg (66.9%) and IV-150 mg (69.6%) groups vs. placebo (55.7%). This was driven primarily by non-serious infections and

infestations (mainly nasopharyngitis), which was the most frequently affected primary SOC. Comparable crude incidence rates of serious AEs and discontinuations due to AEs were reported in the placebo group compared with either secukinumab dose group up to Week 16.

Over the entire treatment period, treatment-emergent AEs were reported with a higher incidence in the Any 150 mg group (85.1%) than in the Any 75 mg group (76.5%), which included patient originally randomized to placebo who were later re-randomized to either dose of secukinumab from Week 16 onward. This difference was driven primarily by non-serious infections and infestations (mainly nasopharyngitis, pharyngitis, influenza, rhinitis). The rate of SAEs was similar between the two secukinumab regimens (10.1% in the Any 75 mg group and 9.4% in the Any 150 mg group).

3.6.1.2 Study CAIN457F2310 in ankylosing spondylitis (AS)

This 5-year double-blind, placebo-controlled study randomized 219 patients with moderate to severe ankylosing spondylitis (AS) despite current or previous NSAIDs, DMARDs and/or TNF-α inhibitor therapy to Secukinumab 75 mg s.c. load (baseline, Weeks 1, 2, and 3) and 75 mg sc maintenance (every 4 weeks starting at Week 4) (n=73); secukinumab 150 mg s.c load and maintenance (n=72); or placebo load and maintenance (n=74). At Week 16 all placebo patients were re-randomized 1:1 to 75mg or 150mg s.c. maintenance dose regimen.

An interim analysis with a cut-off date of 04-Aug-2014 was performed when the last patient completed Week 52 of the study. Efficacy results at Week 52 and safety data up to the cut-off date for all patients (regardless of study visit at the time) are described below.

Secukinumab 150 mg s.c. demonstrated a rapid onset of response and superior efficacy over placebo in measures of disease signs and symptoms, physical function, quality of life and objective markers of inflammation. The secukinumab 150 mg sc load and maintenance dose group, but not the 75 mg sc load and maintenance dose group, had significantly greater responses than placebo at Wk 16, with respect to the primary endpoint (ASAS 20; 61.1% for SC-150 mg vs 27.0% for placebo) and all secondary endpoints (ASAS 40, hsCRP, ASAS 5/6, BASDAI, SF-36 PCS and ASQoL) except for ASAS partial remission. Secukinumab was efficacious through 16 weeks of treatment in both anti-TNF-α naive patients and patients with an inadequate response or intolerance to prior anti-TNF-α therapy. Concerning ASAS40, Secukinumab 150 mg s.c. was superior to placebo at Week 16, with a rate of 36.1% (adjusted p=0.0008) vs. 10.8% for placebo, while 75 mg s.c. (26.0%) was not significant. All treatment responses on primary and secondary variables at Week 16 were sustained through Week 52, with higher response rates observed for 150 mg s.c compared with 75 mg s.c. for nearly all efficacy endpoints.

Higher ASAS 20 and ASAS 40 response rates for secukinumab vs. placebo were observed regardless of previous TNF-α use. TNF-α inhibitor naive patients had numerically higher rates of ASAS 20 response (150 mg: 68.2%; 75 mg: 51.1%, placebo: 31.1%) and ASAS 40 response (150 mg: 43.2%; 75 mg: 31.1%, placebo: 17.8%) than TNF-α inhibitor inadequate responder patients (ASAS 20: 50.0% for 150 mg, 25.0% for 75 mg and 24.1% for placebo; ASAS 40: 25.0% for 150 mg, 17.9% for 75 mg and 0.0% for placebo), with consistently higher response rates for 150 mg compared with 75 mg.

The safety profile of secukinumab in this study showed no new or unexpected safety signals.

One patient in the secukinumab 75 mg group who had a history of CAD, a significant smoking history, and elevated LDL and lipoprotein A levels at baseline died from an acute myocardial infarction on Day 22, which was not suspected to be related to study treatment.

AE incidence up to Week 16 was higher in the secukinumab 150 mg group (65.3%) compared with the secukinumab 75 mg s.c. group (57.5%) and comparable to the placebo group (63.5%). The AE rate in the secukinumab 150 mg s.c. group was driven primarily by non-serious infections (mainly nasopharyngitis). Rates of SAEs and discontinuations due to AEs up to Week 16 were low and comparable in the secukinumab groups compared with the placebo group.

Over the entire treatment period, treatment-emergent AE rates were comparable between the 2 secukinumab dose groups (83.8% patients in the Any secukinumab 75 mg s.c. group and 82.1% in the Any secukinumab 150 mg s.c. group). SAE rates over the entire treatment period were similar between the two secukinumab dose groups (8.6% with the Any 75 mg group and 7.5% with the Any 150 mg group).

Over the entire treatment period, a slightly higher proportion of patients in the Any-secukinumab-150 mg s.c. arm (5.7%) discontinued due to an AE compared to the Any-secukinumab-75 mg s.c. arm (3.8%). All AEs that led to discontinuation were single events with no trends across treatment arms. No patient discontinued due to an infection event.

Based on the benefit-risk profile of secukinumab in AS and other approved indications, it is considered appropriate to initiate this study.

The benefit-risk profile of Secukinumab in AS and other approved indications remains favorable and unchanged. It is therefore considered appropriate to initiate this study.

4 Population

Men and women ≥ 18 years of age who fulfill the modified New York criteria for AS (described in Appendix 3) and have active disease as defined by a BASDAI ≥4 on a scale of 0-10 and spinal pain (BASDAI Question 2) of ≥4 cm on a 0–10 numeric rating scale will be included.

The study will be a multi-centric study planned to be conducted across 30-45 sites in Germany. The study is aimed to randomize a total of approximately 204 patients. Due to statistical adaptions, the required amount of randomized patients can be reduced to a total of approximately 190.

Subjects may be re-screened but no study-related re-screening procedure should be performed prior to written re-consent by the subject.

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 a written, signed and dated informed consent before any study assessment is performed
2. Male or non-pregnant, non-lactating female patients at least 18 years of age
3. Diagnosis of active 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 total BASDAI ≥ 4 (0-10) **at baseline**
5. Spinal pain as measured by BASDAI Question 2 ≥ 4 cm on a 0-10 cm numeric rating scale **at baseline**
6. Total back pain as measured by VAS ≥ 40 mm (0-100 mm) **at baseline**
7. Patients should have been on at least 2 different NSAIDs at the highest recommended dose for at least 4 weeks in total in the past, prior to randomization, with an inadequate response or failure to respond, or less if therapy had to be reduced due to intolerance, toxicity or contraindications
8. Patients must report regular intake of NSAIDs of at least 50% of the highest recommended dose at Screening. Patients with prior TNFα inhibitor therapy must report regular intake of NSAIDs of at least 50% of the highest recommended dose at baseline after the appropriate washout
9. Patients are required to be on a stable dose of NSAIDs for at least 2 weeks before randomization
10. Patients who have previously been on a TNFα inhibitor will be allowed entry into study after an appropriate wash-out period prior to randomization:
    - 4 weeks for Enbrel® (etanercept) – with a terminal half-life of 102 ± 30 hours (s.c. route)
    - 8 weeks for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (i.v. infusion)
    - 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
11. Patients who have been on a TNFα inhibitor (not more than two) must have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months prior to randomization or have been intolerant to at least one administration of an anti-TNFα agent. No more than 40% of patients may have previously received anti-TNFα agents
12. Patients taking MTX (≤ 25 mg/week) or sulfasalazine (≤ 3 g/day) are allowed to continue their medication and must have taken it for at least 3 months and be on a stable dose for at least 4 weeks prior to randomization
13. Patients on MTX must be on stable folic acid supplementation before randomization
14. 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
15. 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. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

3. 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
4. Patients taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine)
5. Previous exposure to Secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor
6. Use of any investigational drug and/or devices within 4 weeks of randomization, or a period of 5 half-lives of the investigational drug, whichever is longer or participation in another clinical study (interventional or non-interventional) in the same indication during enrollment in this study
7. History of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes
8. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization
9. Any intramuscular corticosteroid injection within 2 weeks before randomization
10. Patients previously treated with any biological immunomodulating agents, except those targeting TNFα
11. Patients who have taken more than two anti-TNFα agents
12. Previous treatment with 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)
13. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test
14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during entire study or longer if required by locally approved prescribing information (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 patient. 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 patients on the study, the vasectomized male partner should be the sole partner for that patient
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
    - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
    - 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 benefit of Secukinumab therapy, including inflammatory bowel disease or uveitis
16. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions, which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in an 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 unable to perform self-care
18. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria:
    - Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out lab error.
    - If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.
19. History of renal trauma, glomerulonephritis, or 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 prior to randomization (exception: common cold)
22. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5 mm or according to local practice/guidelines) or a positive QuantiFERON TB-Gold test as indicated in the assessment schedule in Table 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 human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening or randomization

24. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)
25. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the 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. Inability or unwillingness to receive injections with PFS
28. Any medical or psychiatric condition which, in the Investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol
29. Donation or loss of 400 mL or more of blood within 8 weeks before dosing
30. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization
31. Plans for administration of live vaccines during the study period or 6 weeks prior to randomization
32. Patients who are intolerant to NSAIDs

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Novartis/CRO will supply the following study treatments:

- Investigational treatment:
  - Secukinumab 150 mg provided in a 1 mL PFS (1 PFS for 150 mg dose)
- Reference therapy:
  - Secukinumab placebo (Placebo) provided in a 1 mL PFS

At the BSL visit, patients will be instructed by the site staff, utilizing the IFU, on how to self-inject using a PFS. Patients will be asked to raise any questions and then to proceed with self-injection. At the Week 1 visit, patients will be asked to refer to the IFU and to proceed directly with self-injection of the study drug (i.e., no prior retraining) for the remainder of the trial. However, if the patient is not comfortable self-injecting the study treatment, then the site staff may administer it for the patient. From Week 3, patients will be allowed to self-administer the study treatment at home during the optional visits in which there are no scheduled assessments at the site (see Table 6-1 below). If the patient is not comfortable self-injecting the study treatment, then a caregiver may administer it for the patient or the patient can come to the site at an optional visit to have the study drug administered by the study staff.

Note: The Secukinumab PFSs are packed in double-blinded fashion until the end of the trial and therefore, 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 AIN457 150mg/1mL/Placebo.

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

5.1.2 Additional study treatment

Continuation of the concomitant administration of NSAIDs as prescribed before inclusion into the trial is planned beyond the investigational treatment to evaluate the extent of NSAID sparing effect of Secukinumab in this trial.

5.2 Treatment arms

Patients will be assigned to one of the following three treatment arms in a ratio of 1:1:1.

- **Group 1:** Secukinumab 150 mg s.c. at Week 0, 1, 2, 3, 4, 8, 12, 16 and 20; Placebo injections at Week 5, 6, 7 and 17, 18, 19 to maintain the blind for the initial treatment assignment
- **Group 2:** Placebo at Weeks 0, 1, 2, 3 followed by Secukinumab 150 mg s.c. at Week 4, 5, 6, 7, 8, 12, 16 and 20 with Placebo at Week 17, 18, 19 to maintain the blind for the initial treatment assignment
- **Group 3:** Placebo at Weeks 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. From Week 16, patients will be switched to receive Secukinumab 150 mg s.c. at Week 16, 17, 18, 19, and 20

5.3 Treatment assignment, randomization

At baseline visit, all eligible patients will be randomized via Interactive Response Technology (IRT) to 1 of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

From Week 16 onwards, all patients will receive Secukinumab 150 mg. Those patients originally randomized to placebo will self-inject Secukinumab 150 mg after Week 16 at Week 17, 18, 19 and 20, while patients originally randomized to either of the Secukinumab groups will receive their next Secukinumab injection at Week 20 with Placebo injections at weeks 17, 18, 19 to maintain the blinding of initial treatment assignment.

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

Original treatment assignment, as per baseline randomization, will remain double-blinded to the patient, investigator, and site personnel until after the Week 24 database lock and analyses.

5.4 Treatment blinding

This is a double-blind randomized treatment trial. However, after completion of Week 16 assessments of the primary endpoint, patients initially randomized to placebo will be switched to receive Secukinumab 150 mg s.c. every week with intermittent placebo injections in both active arms at weeks 17, 18, 19 to maintain the blind for the initial treatment assignment.

Until the end of the trial, all original randomized treatment assignments will be double-blinded to patients, investigators, and site personnel.

Unblinding of treatment dose or original randomized treatment assignment will only occur in the case of patient emergencies (see Section 5.5.12).

The hsCRP results from samples collected during the treatment period will not be revealed to the site.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the IRT. Upon signing of the ICF by the patient, the investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Only the assigned patient number should be entered in the field labeled "Patient ID" on the EDC data entry screen. Once assigned to a patient, the Patient ID will not be reused. If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Log, and the Demography eCRF should also be completed.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with study treatment in packaging of identical appearance.

The study treatment packaging for Secukinumab/placebo has a 2-part label. A unique medication number is printed on each part of this label. Investigator staff will identify the investigational treatment package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s).

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all 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. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will be in German and comply with the legal requirements of Germany. They will include storage conditions for the study treatment but no information about the patient except for the medication number. The PFS (150 mg active/placebo) sealed in an outer box must be stored in a access controlled/locked refrigerator between 2°C and 8°C and protected from light. They must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations. The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

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

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

5.5.3.2 Handling of other study treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Study treatment (150 mg Secukinumab and placebo) will be administered s.c. by 1 mL PFS throughout the study as 1 mL/150 mg Secukinumab or 1 mL placebo, respectively. Administration of study treatment will occur via self-injection by the patient from Baseline through to Week 20. Administration of study treatment must occur after the study assessments for the visit have been completed. The PFS with the ready-to-use study treatment solution will be provided by the site staff to the patient. Detailed instructions on the self-administration of the study treatment will be described in the IFU for Secukinumab and provided to each patient.

At the Baseline visit, patients will be instructed by the site staff, utilizing the IFU, on how to self-inject using a PFS. Patients will be asked to raise questions, if they have any, and then to proceed with self-injection. At the Week 1 visit, patients will be asked to refer to the IFU and to proceed directly with self-injection of the study drug (i.e. no prior retraining) for the remainder of the trial. However, if the patient is not comfortable self-injecting the study treatment, then the site staff may administer it for the patient.

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

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

Subcutaneous administration with pre-filled syringe (PFS)

Secukinumab solution for s.c. injection (150 mg in 1 mL active/placebo) will be provided in a PFS.

The study treatment solution must be injected into normal areas of the skin.

Patients will be instructed by the site staff on how to self-inject study treatment using a PFS, following the IFU. After training at the Baseline visit, the injections will be self-administered into an appropriate site of the body (thighs, arms, abdomen), and each injection should be given at a different injection site to reduce the risk of injection reaction. Each new injection should be given at least 2.5 cm from the previously used site. If the patient chooses the abdomen, the area 5 cm around the navel should be avoided. Investigational drug should not be injected into areas where the skin is tender, bruised, red, or hard, or where patient has scars or stretch marks. Injection sites should be rotated among appropriate sites to reduce the risk of injection reactions.

The PFSs with study treatment solution should be kept at 2 to 8°C, protected from light and should not be stored frozen. Prior to administration the boxes containing the PFSs with study treatment solution should be allowed to come to room temperature unopened for about 20 minutes before administration. Used PFSs should be disposed immediately after use in a sharps container or according to the regulatory needs of the respective countries.

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

5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational treatment dose adjustments are not permitted.

Investigational treatment interruption is only permitted if, in the opinion of the investigator, a patient is deemed to be placed at a significant safety risk unless administration of investigational treatment is temporarily interrupted. In such cases study treatment should be interrupted only during the time that this risk is present and ongoing. Investigational 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 Rescue medication

Rescue medication is defined as any new therapeutic intervention or a significant change to ongoing therapy made because a patient is experiencing either no benefit from participation in the trial or worsening/exacerbation of their disease. Rescue medication must not be used before completion of Week 12 assessments. Although no patient will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, if rescue with prohibited biologics (as described in Section 5.5.8) occurs, patients 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 patients who are deemed not to be benefiting from the study treatment based upon safety and efficacy assessments by the investigator or for any reason on their own accord will be free to discontinue the study at any time. Changes in NSAID concomitant therapy are permitted after Week 4 assessments and should ideally be performed according to the non-binding NSAID tapering guidelines provided to the patient at the week 4 visit. Please see Section 5.5.7 and Section 5.5.8 for details.

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

5.5.7 Concomitant treatment

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

Patients taking MTX (up to 25 mg/week) must be on a stable dose for at least 4 weeks before randomization and maintained stable until Week 12, except if MTX-related adverse events develop.

Folic acid

Patients 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 may be considered. Cholestyramine could 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 3 healthy volunteers. The administration of cholestyramine is recommended in patients who

require a drug elimination procedure. If a patient receives 8 g t.i.d. for 11 days he/she could be safely randomized 4 weeks after the beginning of the 11- day treatment period.

Systemic corticosteroids

Treatment with systemic corticosteroids is permitted up to a maximum daily 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 12, although the corticosteroid dose should not be reduced by more than 1 mg prednisone equivalent every 4 weeks.

After Week 12, the dose and regimen of systemic corticosteroids may be modified as per investigator's judgment and patient need.

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

Intra-articular corticosteroids are not permitted within the 4 weeks preceding randomization and up to Week 12. After Week 12, 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 20-week period. Injection of intra-articular steroids is not permitted within 8 weeks prior to Week 20.

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

Patients regularly using NSAIDs, low strength opioids, or paracetamol/acetaminophen should be on stable dose for at least 2 weeks before randomization to allow inclusion. They should remain on a stable dose in the study up to Week 4.

Changes in the NSAID intake will be captured by the patient in the patient diary and checked and be transferred into the eCRF at all scheduled study visits after week 4.

Patients taking 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 12 assessments are completed, a change in the low strength opioids, or paracetamol/acetaminophen treatment regimen is permitted.

Any change of the 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

Use of the treatments displayed in Table 5-1 is NOT allowed after the start of the washout period unless otherwise specified below.

Live vaccines should not be given until 12 weeks after last study treatment administration.

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 (until Week 12)	4 weeks
Other DMARD (except MTX or sulfasalazine)	4 weeks
Leflunomide	8 weeks
Leflunomide with cholestyramine washout	4 weeks
Systemic corticosteroids > 10 mg prednisone equivalent** (until Week 12)	2 weeks
Intra-articular steroids injections (until Week 12)	4 weeks
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

Patients may voluntarily discontinue investigational treatment for any reason at any time.

Patients who prematurely discontinue the study should undergo an end of treatment visit (corresponds to the Week 20 visit and also return for the end of study visit at Week 24 (4 weeks after last study treatment (see Table 6-1). The final follow-up visit (Week 24) should be performed before any new treatment is initiated. Study treatment discontinuation must also be recorded in the eCRF and in the IRT.

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

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

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 patient. The following circumstances **require** study treatment discontinuation:

- Withdrawal of informed consent
- Emergence of the following AEs:
  - 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 patient at a safety risk for continuation in the study (A general guidance on clinically notable laboratory values is provided in Appendix 1).
- Pregnancy
- Use of any biologic immunomodulating agent except Secukinumab
- Any protocol deviation that results in a significant risk to the patient's safety

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

For patients who discontinue study treatment, a Dosage Administration Record eCRF should be completed, giving the date and primary reason for stopping study treatment.

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

5.5.10 Withdrawal of consent

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

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts and does not allow analysis of already obtained biologic material.

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information. Investigational 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 communicating or follow-up.

5.5.11 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be formally considered lost to follow-up until his/her scheduled end of treatment visit would have occurred.

5.5.12 Emergency breaking of assigned treatment code

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, investigational 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 be able to unblind details of the investigational drug treatment for the specified patient in the IRT system.

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

Study patient must be discontinued after emergency unblinding.

As per Novartis standard operating procedures (SOPs) it is one of the primary responsibilities of each investigator to be available in case of an urgent emergency unblinding for one of his/her patients.

5.5.13 Study completion and post-study treatment

A patient will be considered to have completed the study if he/she received a maximum of 20 weeks of study treatment and upon completion of the scheduled study assessments and procedures up to and including the follow up visit (Week 24).

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

In any case, the investigator or site staff must contact the IRT as soon as possible to record the patient's study completion (Week 24) and/or discontinuation.

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

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis for any reason specified in the clinical trial study contract. Should this be necessary, the patient should be seen as soon as possible and treated 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 sponsor will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the Visits are performed.

For visits scheduled through Week 4, the study treatment should not be administered less than 7 days after the previous administration. For visits scheduled after Week 4, the study treatment should not be administered less than 14 days after the previous administration. At a minimum, patients will be contacted for safety evaluations during the 30 days following the end of treatment visit at Week 20, including a final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the source documentation.

Subjects who prematurely discontinue should return for the End-of-treatment visit (corresponds to the week 20 visit) 4 weeks after the last study treatment administration, as well as return for the follow-up (week 24). 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 (up to 10 weeks) in duration based on the time required to washout prior anti-rheumatic and other medications and will have a duration, during which time the patient will sign the informed consent form (ICF), be evaluated for eligibility and sufficient time is allowed for potential medication washout, in addition to all other assessments indicated in Table 6-1.

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

The rationale is that in all cases Screening Visit 2 must occur within the 4 weeks prior to randomization and should ideally be performed no less than 2 weeks prior to randomization to allocate time for laboratory analyses and shipment of medication.

All patients evaluated at Screening Visit 1 and 2 for eligibility should not be screen failed on the basis of a medication requiring washout, unless the patient will be unable to complete the washout in the appropriate time frame before randomization.

Table 6-1 Assessment schedule

	Screening[1]		Treatment 1										Treatment 2					Follow Up
	Screening Visit 1	Screening Visit 2																
Week	**-10 to -4**	**-4 to -2**	**BSL**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**	**16**	**17**	**18**	**19**	**20**	**F24**
Obtain informed consent	X																	
Optional Site visit						X		X		X				X	X	X		
Inclusion/Exclusion criteria[2]	X	X	X															
Relevant medical history/ current medical condition	X	X	X															
Prior medication	X	X	X															
AS assessment[3]	X																	
Demography	X																	
Cardiovascular medical history		X																
Smoking history		X																
ECG[4]		X										X						
Physical exam[4]		X	X		X		X		X		X	X	X				X	X
Height, weight		X																
Vital signs	X	X	X		X		X		X		X	X	X				X	X

	Screening[1]		Treatment 1										Treatment 2					Follow Up
	Screening Visit 1	Screening Visit 2																
Week	**-10 to -4**	**-4 to -2**	**BSL**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**	**16**	**17**	**18**	**19**	**20**	**F24**
PPD skin test[5] or QuantiFERON TB-Gold test		X																
Chest X-ray or MRI[6]		X																
Hematology, blood chemistry, urinalysis		X	X		X		X				X	X	X				X	X
Serum pregnancy test		X																
Urine pregnancy test			X				X				X	X					X	X
Randomization			X															
Administration of s.c. study treatment via PFS			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication/ non-drug therapy	X	Update as necessary																

	Screening[1]		Treatment 1										Treatment 2					Follow Up
	Screening Visit 1	Screening Visit 2																
Week	**-10 to -4**	**-4 to -2**	**BSL**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**	**16**	**17**	**18**	**19**	**20**	**F24**
Adverse events/SAEs (if applicable, including injection site reactions)[7]	X																	
NSAID intake reported in eCRF		X	X	X	X	X	X											X
Provide NSAID Diary to patient and instruct patient							X				X	X	X					
NSAID intake captured in patient diary								X	X	X	X	X	X	X	X	X	X	
Check NSAID diary									X		X	X	X				X	
Patient's global assessment of disease activity (VAS)			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
BASFI			X	X	X		X		X		X	X	X				X	X

	Screening[1]		Treatment 1										Treatment 2					Follow Up
	Screening Visit 1	Screening Visit 2																
Week	**-10 to -4**	**-4 to -2**	**BSL**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**	**16**	**17**	**18**	**19**	**20**	**F24**
BASDAI			X	X	X		X		X		X	X	X				X	X
Spinal mobility (BASMI Linear + chest expansion)			X		X		X				X	X	X				X	
SF-36			X				X					X					X	
ASAS Health Index			X				X					X					X	
Erythrocyte Sedimentation Rate (ESR)		X	X		X		X				X	X	X				X	X
High sensitivity C-reactive protein (hsCRP)		X	X		X		X				X	X	X				X	X
HLA-B27			X															

[1] If the patient'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 Baseline (BSL) / Day 1'. The data for all three visits should be recorded on the corresponding eCRFs available at SV1.

[3] The following eCRFs are to be completed: AS Disease background eCRF, Modified New York criteria for AS eCRF

[4] These assessments are source documentation only and will not be entered into the 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.

	Screening[1]		Treatment 1										Treatment 2					Follow Up
	Screening Visit 1	Screening Visit 2																
Week	**-10 to -4**	**-4 to -2**	**BSL**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**	**16**	**17**	**18**	**19**	**20**	**F24**

[6] 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 patient meets inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation. The X-ray may be replaced by an MRI assessment.

[7] AEs/SAEs occurring after the patient has signed the informed consent must be captured on the appropriate eCRF page. SAEs must be recorded from signing of informed consent, AEs must be captured from the BSL visit on.

* For all patients who discontinue or withdraw from the study, the investigator should ensure that the patient completes an end of treatment visit.

6.1 Information to be collected on Screening failures

Patients may discontinue from the study prior to randomization. These patients are considered Screening failures.

If a patient discontinues before entering the double-blind treatment period at baseline, the 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 demography data, the reason for failing (screening failure log) and informed consent will be collected for those patients who fail to enter the treatment phase.

Reporting of potential SAE which may have occurred from time of signing informed consent until screening failure time should be followed as described in Section 7.2

6.2 Patient demographics/other baseline characteristics

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

- Year of birth, age, sex, race and source of patient referral
- Relevant AS and general medical history/current medical condition data until the start of study treatment, number 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 will be entered in the Prior/Concomitant medications or Significant non-drug therapies eCRF page.

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

6.4 Efficacy

- Assessment of SpondylArthritis International Society criteria (ASAS)20
- ASAS-NSAID score
- 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)
- Spinal mobility assessed by Bath Ankylosing Spondylitis Metrology Index (BASMI)

- hsCRP and ESR

6.4.1 Assessment of ASAS-NSAID score

The ASAS-NSAID score will be calculated in accordance with the ASAS recommendations (Dougados et al 2011). NSAID intake will be collected in accordance with the ASAS recommendations (i.e., name, mean dose, number of days of intake during a period of time). Thereafter, the ASAS-NSAID score will be calculated considering both the daily dose of the specific NSAID(s) and the percentage of days of intake of the NSAID(s) during a given period of time.

Detailed information for calculating the ASAS-NSAID score is given in Appendix 4.

6.4.2 Assessment of SpondyloArthritis International Society criteria (ASAS)

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

The main ASAS domains are as follows:

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

The additional assessment domains are as follows:

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

Investigator must review the results timely and document adverse events, if applicable.

ASAS Response Criteria-20% (ASAS20)

ASAS20 response is defined as an improvement of ≥ 20% and ≥ 1 unit on a scale of 10 in at least 3 of the 4 main domains and no worsening of ≥ 20% and ≥ 1 unit on a scale of 10 in the remaining domain.

6.4.2.1 ASAS Response Criteria-40% (ASAS40)

ASAS40 response is defined as an improvement of ≥40% and ≥2 units on a scale of 10 in at least three of the four main domains and no worsening at all in the remaining domain.

6.4.2.2 ASAS 5/6 improvement criteria

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

6.4.2.3 ASAS partial remission criteria

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

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

The patient's global assessment of disease activity will be performed using a 100 mm visual analog scale (VAS) ranging from not severe to very severe, after the question, *"How active was your disease on average during the last week?*".

6.4.4 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, after the question "*Based on your assessment, please indicate what is the amount of back pain at any time that you experienced during the last week?*" and *"Based on your assessment, please indicate what is the amount of back pain at night that you experienced during the last week?"*

6.4.5 Bath Ankylosing Spondylitis Functional Index (BASFI)

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

6.4.6 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

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

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

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

6.4.7 Bath Ankylosing Spondylitis Metrology Index (BASMI linear)

The BASMI is a validated instrument that uses the minimum number of clinically appropriate measurements that assess accurately axial status, with the goal to define clinically significant changes in spinal movement. Parameters include:

1. Lateral spinal flexion
2. Tragus-to-wall distance
3. Lumbar flexion (modified Schober)
4. Maximal intermalleolar distance
5. Cervical rotation angle

Additionally, the following assessments should be taken:

6. Chest expansion
7. Occiput-to-wall distance

Detailed information on the assessments is described in Appendix 4.

6.4.8 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 1993). Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed (Ware 1994). The SF-36 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual patients.

The purpose of the SF-36 in this study is to assess the health-related QoL of patients. Given the acute nature of this disease, version 2, with a 1-week recall period, will be used in this study. Investigator must review the results timely and document adverse events, if applicable.

6.4.9 ASAS Health Index

The ASAS Health Index (ASAS HI) is an index that measures an individual's status of functioning, disability and health in individuals and is designed specifically for spondyloarthritis patients. (ASAS HI) (12).

The ASAS HI is a linear composite measure that contains 17 items of functioning and health and 9 environmental factors addressing categories of support/relationships, attitudes and health services with dichotomous response options: "I agree" and "I do not agree". The result forms a unidimensional scale providing a sum score representing a wide spectrum of different levels of functioning (Kiltz et al. 2014).

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 response to treatment.

Since the results of this test may unblind study personnel, results from the central laboratory 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.

6.4.11 Erythrocyte sedimentation rate (ESR)

ESR is helpful in diagnosing inflammatory diseases and is used to monitor disease activity and response to therapy. ESR will be performed locally at the investigative site using a centrally provided assessment kit.

6.4.12 Appropriateness of efficacy assessments

The ASAS-NSAID score is used to determine the NSAID sparing effect of biologic i.e. the timing of discontinuation/tapering of NSAID(s) after initiating treatment with Secukinumab.

The other efficacy outcome measures used in this study are the standard measures used across all AS trials.

6.5 Safety

- QuantiFERON TB-Gold test or PPD skin test
- Chest X-ray or MRI
- Physical examination
- Vital signs
- Height and weight
- Laboratory evaluations
- Pregnancy and assessment of fertility
- Local tolerability (injection site reactions)
- Tolerability of Secukinumab

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

6.5.1 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 country 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 patient's eligibility for the trial. The test will be used to screen the patient population for latent tuberculosis infection.
- The test will be analyzed by the central laboratory. Details on the collection, processing and shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual.

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.

Because the reaction (induration) will take 48-72 hours to develop, the patients must return to the study center 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 Chest X-ray or MRI

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

6.5.3 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 which meet the definition of an SAE must be recorded in the Adverse Event eCRF. All findings meeting the definition of an AE must be recorded from the first administration of study drug on.

6.5.4 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.

6.5.5 Height and weight

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

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

6.5.6 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected as listed in the sub-sections below (except for urinalysis and ESR). Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE CRF page as appropriate. All patients with laboratory tests containing clinically significant abnormal values are to be followed until

the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

Clinically notable laboratory results are defined in Appendix 1.

6.5.6.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential counts, and platelet count will be measured at scheduled visits.

6.5.6.2 Clinical chemistry

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

6.5.6.3 Urinalysis

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

6.5.7 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as indicated in Table 6-1.

ECGs can be performed externally at a qualified physician but the investigator/qualified site staff must review the tracing. The tracing must then be stored with the subject's source documents. If the ECG findings at screening are clinically relevant and would prevent the subject from participating in the study (taking into account the subject's overall status as well as the medication profile), the subject should be recorded a screen failure and should not receive treatment. Findings at the later ECG readings will be reported as adverse or serious adverse events. If these findings constitute a reason for premature patient withdrawal or would render the overall risk-benefit evaluation of continued participation and treatment in the study unfavorable for the patient, the patient must discontinue study medication.

6.5.8 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum β-hCG test (serum pregnancy test) performed at the second Screening visit 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.

6.5.9 Local tolerability (Injection site reactions)

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

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

6.5.10 Tolerability of Secukinumab

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

6.5.11 Appropriateness of safety measurements

The safety measures used in this study are reliable and relevant standard measures for a biologic in AS. According to local recommendations, a chest X-ray should be performed in clinical practice before initiation of an immunomodulating biologic therapy for AS (DGRh 2009). The radiation exposure that results from the chest X-ray safety measurements at Screening are estimated to be far below 1 mS. For effective radiation doses under 3 mS (300 mrem), the risk is considered to be minimal. Therefore, the radiation exposure in this study involves minimal risk and is necessary to ensure reliable safety measures before the treatment with a biologic.

While hsCRP results are not automatically communicated to the site by the central lab, it will be acceptable to perform a CRP measurement at a local lab in case this is warranted for safety reasons.

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

6.6 Other assessments

- HLA-B27

6.6.1 HLA-B27

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

6.6.2 Resource utilization

No measures of Healthcare Resource Utilization (RU) will be collected in the study.

6.6.3 Pharmacokinetics

Not applicable.

6.6.4 Other biomarkers

Not applicable.

7 Safety monitoring

7.1 Adverse events

An AE is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after first intake of study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drugs under evaluation that are given during any period of the study.

Medical conditions/diseases present before first intake of study drug are only considered adverse events if they worsen after study start. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, require dose reduction or temporary or permanent study drug discontinuation or require therapy.

All AEs with a date of onset up to 30 days following after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported.

The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. AEs may also be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

All AEs should be treated appropriately. Treatment may include 1 or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the AE should be recorded on the Adverse Event CRF.

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

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

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any 1 of the following criteria:

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

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

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

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent 1 of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

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

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per Section 7.2.2.

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

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. For patients who discontinue study medication, SAEs still need to be reported until the end of study, regardless of their suspected relationship to study medication.

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 is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the German Novartis Clinical Safety & Epidemiology Department. The SAE form should also include information about the concomitant NSAID medication. The telephone and telefax number of the contact persons in the German department of Clinical Safety and Epidemiology, 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.

All SAEs occurring during the follow-up period will be entered in the Adverse Events CRF pages. In addition, an SAE Report Form should be completed. Follow-up information will be sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

Adverse reactions under a Novartis drug of which investigator became aware prior to or during Screening and which were not yet reported should be forwarded to the local Novartis Clinical Safety & Epidemiology Department. This adverse reaction report including the administered Novartis drug and causality assessment should be forwarded independently from the described procedure. Serious adverse reactions occurring under non-Novartis drugs which are not investigational medicinal product (IMP) should be forwarded either to the national competent authority (BfArM or PEI), the Drug Commission of the German Medical Association or the respective marketing authorization holder.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Clinical Safety & 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 drug 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 Directive2001/20/EC or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

Secukinumab has not been studied specifically in patient with hepatic impairments. No pharmacokinetic data are available in these patients. However IgGs are mainly eliminated via catabolism and hepatic impairment is not expected to influence clearance of Secukinumab.

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

The following two categories of abnormalities / adverse events have to be considered during the course of the study:

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

Please refer to Table 13-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 13-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 13-2 in Appendix 2.

For the liver laboratory trigger:

- Repeating the LFT (Liver Function Test) within the next week to confirm elevation.

Repeat laboratory tests should be entered on the appropriate unscheduled local laboratory CRF page.

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

For the liver events:

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

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

7.4 Renal safety monitoring

Secukinumab has not been studied specifically in patient with renal impairments. No pharmacokinetic data are available in patients with renal impairment. The renal elimination of

intact Secukinumab, an IgG monoclonal antibody, is expected to be low and of minor importance.

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

The following two categories of renal adverse events have to be considered during the course of the study:

1. Serum event:
   - confirmed (after ≥ 24h) increase in serum creatinine of ≥ 25% compared to baseline during normal hydration status
2. Urine event: New onset (≥1+) proteinuria, hematuria or glucosuria; or
   - Doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable).

Every renal laboratory trigger or renal event as defined in Table 7-1 should be followed up by the investigator or designated personnel at the trial site as summarized below.

Table 7-1 Specific renal alert criteria and actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50 % compared to baseline	Follow up within 24-48h if possible Consider drug interruption Consider patient hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥ 1+ Albumin- or Protein-creatinine ratio increase ≥ 2-fold Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider drug interruption / discontinuation
New dipstick glucosuria ≥ 1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥ 1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	

Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed

Monitor patient regularly (frequency at investigator's discretion) until either:

Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or

Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

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

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

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

7.6 Prospective suicidality assessment

Not applicable

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/CRO will review the protocol and CRFs with the investigators and their staff. During the study, Novartis/CRO employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the 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 patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis/CRO 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 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 patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff / CRO staff review the data entered into the CRFs 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 (or a designated CRO).

ECG records will be kept at the site as source data.

Diary data will be entered into a paper diary by the patient. The study staff will check the diary and enter the data into the eCRF. The database will be sent electronically to Novartis (or a designated CRO).

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

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

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be

locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Trial Statistician and Statistical Reporting and the Clinical Trial Leader.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

Summary statistics for continuous variables will generally include the number of 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 generally focus on the first 12-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 3 treatment groups. These treatment groups represent the regimens subjects will be eligible to be randomized to.

Secukinumab ("delayed tapering") regimen: Secukinumab 150 mg s.c. at Week 0, 1, 2, 3, 4, 8, 12, 16 and 20; Placebo injections at Week 5, 6 and 7 and 17, 18. 19.

Secukinumab ("early tapering") regimen: Placebo at Weeks 0, 1, 2, 3 followed by Secukinumab 150 mg s.c. at Week 4, 5, 6, 7, 8, 12, 16 and 20 with additional Placebo injections at week 17, 18. 19.

Placebo regimen: Placebo at Weeks 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. From Week 16, patients will be switched to receive Secukinumab 150 mg s.c. at Week 16, 17, 18, 19, and 20.

9.1 Analysis sets

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

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, and in the actual stratum if stratified randomization is used.

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, race, weight, height, and BMI

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

- Duration of disease, TNF- alpha inhibitor status (naïve or inadequate responder), Patient's global assessment of disease activity and other ASAS components, hsCRP, ESR, number of prior biologic AS therapies, dose of methotrexate or other DMARD at randomization

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.

9.3 Treatments

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.

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) and the total duration of exposure to ankylosing spondylitis therapies previously.

9.4 Analysis of the primary variable(s)

Details of the testing strategy including primary and secondary endpoints are provided in Section 9.4.1 and Section 9.5.1.

9.4.1 Variable(s)

The primary efficacy variable is response to treatment according to the ASAS20 criteria at Week 12. The analysis of the primary variable will be based on the FAS subjects. The analysis of the primary variable will be based on the following estimand:

- Analysis set: FAS
- Variable of interest: proportion of patients achieving treatment response as defined by the ASAS20 criteria at Week 12.
- Intervention effect: effect between a secukinumab pooled groups vs. placebo regardless of adherence to randomized treatment.

Summary measure: Odds ratio (OR)

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 in the pooled Secukinumab groups at week 12 versus placebo regimen.

In statistical terms, H_1: $p_1 = p_0$, H_A: $p_1 \neq p_0$, where p_0 and p_1 denotes the proportion of ASAS20 responders at Week 12 in the placebo and pooled Secukinumab groups. .Secukinumab groups will be pooled using their measurements at week 12.

H1: Secukinumab (pooled) is not different to placebo with respect to ASAS20 response at week 12.

The primary analysis will be conducted via logistic regression with treatment, TNF-α status (previously exposed / never exposed), and CRP status (above central lab ULN / equal or below central lab ULN) as factors. The two Secukinumab groups will be pooled using a linear contrast. Odds ratios and 95% CI will be presented comparing Secukinumab (pooled) to placebo.

9.4.3 Handling of missing values/censoring/discontinuations

Missing data for ASAS20 response and other binary efficacy variables (e.g. ASAS5/6, etc.) for data up to Week 20 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 20
2. Subjects who do not have the required data to compute response (e.g. ASAS components) at baseline and at the specific time point will be classified as non-responders.

Patients who were unblinded prior to the scheduled timepoint 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) up to Week 20 will be analyzed using a mixed-effects model repeated measures (MMRM) which is valid under the missing at random (MAR) 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.

Additionally, under the assumption of missing at random, multiple imputation by treatment may be performed for baseline weight as well as for all baseline and post-baseline efficacy variables of interest during the trial.

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 addition, further logistic regression models may be conducted which explore the impact of other baseline or disease characteristics on response.

In case of a substantial number of missing values, their impact on the analysis results may be assessed as well by repeating the logistic regression model using ways to handle missing data. These may include, but are not limited to:

a) Tipping point analysis

b) Observed data analysis

9.5 Analysis of other variables

9.5.1 Secondary efficacy variables

The secondary efficacy variables are listed below. Secondary efficacy variables will be analyzed using the FAS population.

- ASAS20 response at Week 12/16.
- ASAS-NSAID response at Week 12.
- Change from baseline in BASDAI at Week 12/16.
- Change from baseline in SF36 physical component score at Week 12/16.
- Change from baseline in ASAS-NSAID score at Week 12 for Secukinumab (delayed tapering) vs. change from baseline in ASAS-NSAID score at Week 16 for Secukinumab (early tapering)
- Change from baseline in BASDAI at Week 12 for Secukinumab (delayed tapering) vs change from baseline in BASDAI at Week 16 for Secukinumab (early tapering).
- Change from baseline in BASDAI question 2
- ASAS20 response at Week 4 for Secukinumab (delayed tapering) vs. ASAS20 response at Week 20 for placebo group

Testing strategy

The following hypotheses will be included in the testing strategy, and type-I-errors will be set such that a family-wise type-I-error of 5% is kept:

Primary objective:

H_1: Secukinumab 150 mg s.c. (pooled Secukinumab groups) is not different to placebo regimen with respect to signs and symptoms (ASAS20 response) at Week 12

Secondary objectives:

H_2: Secukinumab 150 mg s.c. (pooled Secukinumab groups) is not different to placebo regimen with respect to change from baseline in ASAS-NSAID score at Week 12

H_3: Secukinumab 150 mg s.c. (pooled Secukinumab groups) is not different to placebo regimen with respect to change from baseline in total BASDAI score at Week 12

H_4: Secukinumab 150 mg s.c. (delayed tapering) is not different to placebo regimen with respect to signs and symptoms (ASAS20 response) at Week 12

H_5: Secukinumab 150 mg s.c. (early tapering) is not different to placebo regimen with respect to signs and symptoms (ASAS20 response) at Week 12

H_6: Secukinumab 150 mg s.c. (early tapering) is not different to placebo regimen with respect to signs and symptoms (ASAS20 response) at Week 16

H_7: Secukinumab 150 mg s.c. (delayed tapering) is not different to placebo regimen with respect to change from baseline in ASAS-NSAID score at Week 12

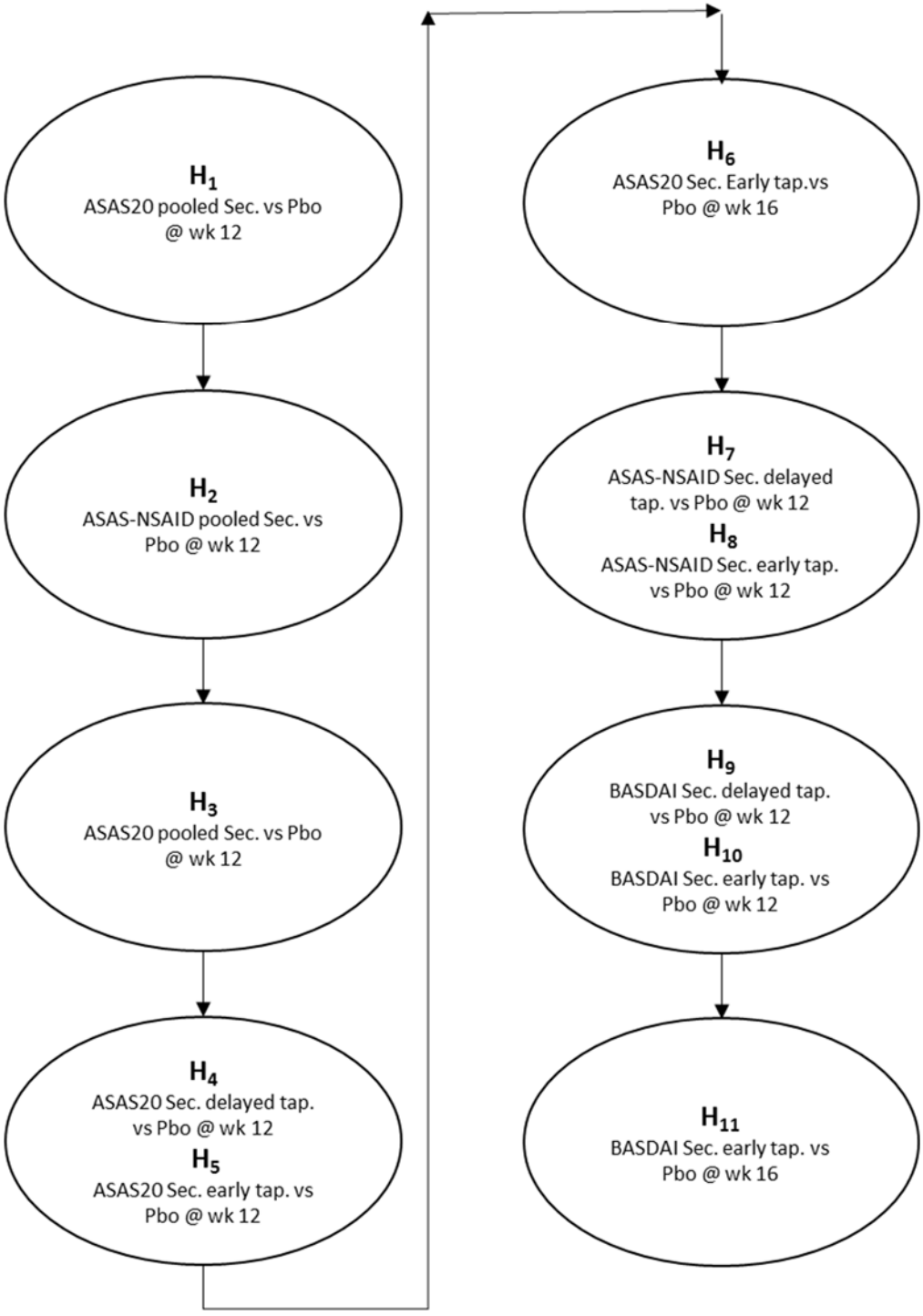
H_8: Secukinumab 150 mg s.c. (early tapering) is not different to placebo regimen with respect to change from baseline in ASAS-NSAID score at Week 12

H_9: Secukinumab 150 mg s.c. (delayed tapering) is not different to placebo regimen with respect to change from baseline in total BASDAI score at Week 12

H_{10}: Secukinumab 150 mg s.c. (early tapering) is not different to placebo regimen with respect to change from baseline in total BASDAI score at Week 12

H_{11}: Secukinumab 150 mg s.c. (early tapering) is not different to placebo regimen with respect to change from baseline in total BASDAI score at Week 16

These hypotheses will in principal be tested hierarchically in ascending order. However, since some hypotheses for individual group comparisons are already contained in the higher-ranked, pooled comparisons for the same endpoint (i.e. H_4 and H_5 are contained in H_1, H_7 and H_8 are contained in H_2 and H_9 and H_{10} are contained in H_3) these individual hypothesis can be tested simultaneously. The justification is that as soon as the pooled hypothesis has been rejected (e.g. H_1), at least one of the two contained individual hypotheses (e.g. H_4 and H_5) must be false and there is only a potential for at most one type-I-error. Therefore H_4 and H_5 can be tested simultaneously once all higher-ranked hypotheses have been rejected. The same argument applies to H_7 and H_8 and to H_9 and H_{10}. The following chart displays the testing strategy graphically:



First the hypotheses (H_1) for the primary objective (ASAS20 for Secukinumab pooled at week 12) versus placebo will be tested. If this hypothesis can be rejected at level α, H_2 will be tested and so on until H_4. H_4. and H_5 will be tested simultaneously. If both can be rejected, H_6 will be tested and so on. As soon as a hypothesis fails to be rejected at level α, all tests of the following hypotheses (except the paired hypothesis in the same knot) will be regarded as exploratory only and will not provide any confirmatory evidence, irrespective of their nominal p-values. Of note, in the description above, rejection of a hypothesis refers to rejection of the two-sided hypothesis; however the level of a rejected hypothesis is only passed on according

to the procedure for the test of another hypothesis if the treatment effect is in favor of the Secukinumab regimen. The family-wise error will be set to α=5% and it will be controlled with the proposed semi-hierarchical testing strategy.

ASAS20 at week 12

Response at Week 12 to ASAS20 for Secukinumab (delayed-tapering) versus placebo will be evaluated using a logistic regression model with treatment as a factor and baseline weight as a covariate.

ASAS20 at week 16

Response at Week 16 to ASAS20 for Secukinumab (early-tapering) versus placebo will be evaluated using a logistic regression model with treatment as a factor and baseline weight as a covariate.

ASAS-NSAID at Week 12

Between-treatment differences in the change in ASAS-NSAID relative to baseline will be evaluated using a mixed-effect model repeated measures (MMRM). Treatment group and analysis visit as factors, baseline ASAS-NSAID and weight as continuous covariates. Treatment by analysis visit and baseline ASAS-NSAID 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 pooled treatment effect will be determined from a linear contrast comparing the (mean of the) two Secukinumab regimens to placebo. The significance of the two individual Secukinumab treatment group effects will be determined from the pairwise comparisons performed between Secukinumab regimens and placebo.

BASDAI at Week 12/16

The change from baseline to Week 12/16 in total BASDAI will be analyzed using a MMRM with treatment regimen 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 Secukinumab treatment effect will be determined from the pairwise comparisons performed between Secukinumab regimens and placebo.

Other secondary variables

SF-36 PCS

For the change in SF-36 PCS, between-treatment differences will be evaluated using a mixed effect repeated measures model (MMRM). Treatment group and analysis visit will be included as categorical factors and baseline SF-36 PCS score and weight as continuous covariates. Treatment by analysis visit and baseline SF-36 PCS 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 Secukinumab treatment effect will be determined from the pairwise comparisons performed between Secukinumab regimens and placebo.

Between-treatment comparisons for binary variables in the FAS population (e.g. ASAS20) at individual analysis visits will be evaluated using a logistic regression model with treatment as a factor and weight as a covariate for any analysis up to end of study.

Continuous variables (e.g. change from baseline in BASDAI question 2) will be evaluated using a MMRM with treatment regimen 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 pairwise comparisons performed between Secukinumab regimens and placebo and/or Secukinumab at the appropriate analysis visits.

9.5.2 Exploratory efficacy variables

The exploratory efficacy variables are listed below. Exploratory efficacy variables will be analyzed using the FAS population.

- Total ASAS-NSAID [Area Under Curve (AUC)] Score from treatment start with Secukinumab to a Secukinumab exposure of 12 weeks.
- Total ASAS-NSAID [Area Under Curve (AUC)] Score From Week 4 to Week 16
- Proportion of patients with no NSAID intake after Secukinumab exposure of 12 weeks
- Proportion of patients with no NSAID intake at week 12.
- Change from Baseline in the ASAS Health Index after Secukinumab exposure of 12 weeks
- Change from Baseline in the ASAS Health Index at week 12
- Change from baseline in BASMI
- ASAS40 response
- ASAS20 response
- ASAS5/6 response
- Change from baseline in hsCRP
- Change from baseline in total BASDAI
- BASDAI 50 response
- ASAS partial remission
- Change from baseline in ASAS components including:
  a. Patient global disease activity
  b. Total spinal pain
  c. Inflammation (average of BASDAI questions 5 and 6)
  d. BASFI
- Change from baseline in ASDAS-CRP and ASDAS-ESR
- ASDAS inactive disease as defined by ASDAS < 1.3
- ASDAS clinically important improvement (change in ASDAS ≥ 1.1) and major improvement (change in ASDAS ≥ 2.0)
- Reasons given in the patient diary on why he was not able to taper NSAIDs despite reduced spinal pain

Secukinumab groups at week 12 (delayed tapering) and week 16 (early tapering) will be compared for all primary, secondary and exploratory variables that have not been outlined. Variables such as hsCRP whose distribution is not anticipated to be normal will be transformed and analyzed on the $\log_e$ scale. All other details and analyses regarding the exploratory efficacy variables will be outlined in the statistical analysis plan.

9.5.3 Safety variables

Adverse events

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

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 will be presented separately by study periods, i.e. Weeks 1-16 and after Week 16.

As appropriate, the incidence of AEs will be 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.

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

Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, 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.

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.

Vital signs

Analysis of the vital sign measurements using descriptive 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.

HLA-B27

Human Leukocyte Antigen-B27 (HLA-B27) will be summarized at baseline and listed.

9.5.4 Resource utilization

Not applicable.

9.5.5 Pharmacokinetics

Not applicable.

9.5.6 Pharmacogenetics/pharmacogenomics

Not applicable.

9.5.7 Biomarkers

Not applicable.

9.5.8 PK/PD

Not applicable.

9.6 Interim analyses

Not applicable.

9.7 Sample size calculation

All sample size and power considerations are performed using EAST 6.

The sample size was calculated based on the phase III results of the MEASURE2 study, which used the same dose and loading regimen as will be applied in this trial. Under the assumption of 56.9% ASAS20 responders in the Secukinumab (delayed tapering) group and 27.0% in the placebo group, a sample size of 62 patients per group is required to have 90% power to show superiority of Secukinumab over placebo at a two sided α=5%.

For the comparison of the the early tapering group at week 16 vs. placebo, the same treatment effect is expected, leading to the same sample size. To compensate for some dropout and other protocol deviations, the sample size will be increased to 68 per arm. The total sample size of this trial will thus be 204. At the time of writing this amendment, about 190 patients have been recruited into this trial and it seems unlikely that a sample > 200 can be recruited within reasonable time. With this sample size, the (newly introduced) comparison of pooled

Secukinumab groups vs. placebo, the trial would still have almost 80 % (78%) power if the placebo response was somewhat higher (35%) than originally assumed..

Other secondary endpoints

It will be assumed that the amount of NSAID reduction observed in the etanercept SPARSE trial (Dougados et al. 2014), of 63.9 vs. baseline (etanercept) and 36.6 for placebo, with an estimated standard deviation of 40 will be seen in this trial for both Secukinumab groups versus placebo. Based on this assumption both secukinmab groups will have >90% power to show superiority over placebo for NSAID reduction.

For the total BASDAI parameter, 62 patients per treatment group should yield a power of approximately 91%, assuming a a treatment difference of 1.8 with a standard deviation of 2.8 (van der Heijde 2006). For SF-36 PCS, 62 patients per treatment group yield a power of approximately 87.5%, assuming mean change of 6.9 on both Secukinumab regimen and mean change of 1.6 on placebo with common standard deviation of 8.7 (Davis 2007).

10 Ethical considerations

Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable

regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.
Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

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. 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 an informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study.

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study 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, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of

Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

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 for patients safety may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any 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

Blauvelt A, Prinz J, Gottlieb AB, et al (2014) Secukinumab administration by pre-filled syringe: efficacy, safety, and usability results from a randomized controlled trial in psoriasis (FEATURE). Br J Dermatol.(published online ahead of print August 16, 2014).

Braun et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial; Lancet 2002; 359: 1187–93.

Dougados M, Simon P, Braun J et al (2011) ASAS recommendations for collecting, analysing and reporting NSAID intake in clinical trials/epidemiological studies in axial spondyloarthritis. Ann Rheum Dis;70(2):249-51.

Dougados M, Wood E, Combe B et al (2014) evaluation of the nonsteroidal anti-inflammatory drug-sparing effect of etanercept in axial spondyloarthritis: results of the multicenter, randomized, double-blind, placebo-controlled SPARSE study. Arthritis Res Ther;16(6):481.

Dubreuil M (2014) myocardial infarction risk with diclofenac use in spondyloarthropathy versus non-inflammatory low back pain. ACR/ARHP Annual Meeting 2014; Boston, MA. Arthritis Rheumatol. Supplement 66(10):Abstract no. 554;S243.

Kiltz U, van der Heijde D, Boonen A, Braun J (2014) The ASAS Health Index (ASAS HI) – a new tool to assess the health status of patients with spondyloarthritis; Clin Exp Rheumatol 2014; 32 (Suppl. 85):S105-S108

Konttinen L, Tuompo R, Uusitalo T et al (2007) anti-TNF therapy in the treatment of ankylosing spondylitis: the Finnish experience; Clin Rheumatol (2007)26(10):1693–1700.

Nderitu P, Doos L, Jones PW et al (2013) non-steroidal anti-inflammatory drugs and chronic kidney disease progression: a systematic review. Fam Practice;30(3):247–55.

Poddubnyy D, Hermann KG, Callhoff J et al (2014) ustekinumab for the treatment of patients with active ankylosing spondylitis: results of a 28-week, prospective, open-label, proof-of-concept study (TOPAS); Ann Rheum Dis;73(5):817-23.

Sieper et al. 2015. Secukinumab significantly improves signs and symptoms of active ankylosing spondylitis: 52-Week Data from MEASURE 2, A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial with Subcutaneous Loading and Maintenance Dosing. EULAR Annual Meeting, Rome Italy, 2015. Oral presentation (presentation number 168)

Van der Hejde D, Sieper J, Maksymowych WP et al (2011) update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. Ann Rheum Dis;70(6):905-8.

Van Baarsen LGM, Lebre MC, van der Coelen D, et al (2011) IL-17 levels in synovium of patients with rheumatoid arthritis, psoriatic arthritis and osteoarthritis: Target validation in various forms of arthritis. Ann Rheum Dis;70:A79.

13 Appendices

13.1 Appendix 1: Clinically notable laboratory values and vital signs

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

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

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

	Final Harmonization

		Notable Criteria	
Laboratory Variable		Standard Units	SI Units
LIVER FUNCTION AND RELATED VARIABLES			
SGOT (AST)		>3 x ULN	>3 x ULN
SGPT (ALT)		>3 x ULN	>3 x ULN
Bilirubin		>2 x ULN	>2 x ULN
Alkaline phosphatase		>2.5 x ULN	>2.5 x ULN
RENAL FUNCTION, 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

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

Table 13-2 Liver event and laboratory trigger definitions

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

Table 13-3 Follow-up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	Discontinue the study drug immediately Hospitalize, if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
ALT or AST		
> 8 × ULN	Discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	Discontinue the study drug immediately Hospitalize, if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	Repeat LFT within 48 hours If elevation persists, continue follow-up monitoring If elevation persists for *more than 2 weeks*, discontinue the study drug Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	Discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	Repeat LFT within 48 hours If elevation persists, establish causality Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	Discontinue the study drug immediately Hospitalize the patient Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
Any AE potentially indicative of a liver toxicity*	Consider study drug interruption or discontinuation Hospitalization if clinically appropriate Establish causality Complete liver CRF	Investigator discretion

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

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

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

13.4.1 Analysis and report of NSAID intake during clinical trials/studies

1. As soon as the information contained in Table 13-4 is available (eg, name, mean dose, number of days of intake during a period of time), the recommendation is to analyse/report the data in terms of NSAID equivalent dose in mg/day on a 0–100 scale. The 150 mg equivalent diclofenac is set to 100. When the exact number of days with NSAID intake is not known (usually when the interval of time between 2 visits exceeds 2 weeks), it is recommended to refer to the semi-quantitative estimation summarised in Table 13-4. In this case, a score of 7/7 is proposed for the answer ‘every day’, 6/7 for >5 days/week, 4/7 for >3 to ≤5 days/week, 2 for >1 to ≤3 days/ week, 0.5 for ≤1 day/week and 0 if the patient did not take any NSAID during the study period (Dougados et al 2011).

The general formula for the calculation is:

(equivalent NSAID score) × (days of intake during period of interest) × (days per week)/(period of interest in days)

For example, if during a period of interest (between 2 visits) of 6 months, the patient has taken piroxicam 20 mg during 4 months and if during this 4-month period he has taken piroxicam 3–5 days per week the calculation is as follows:

100 (20 mg piroxicam score) × 120 (4 months) × 4/7 (3–5 days/week)/180 (6 months) = 38.1

If the patient has used 10 mg piroxicam during the remaining 2 months on 2 days a week, the NSAID score for this period is:

50 (10 mg piroxicam score) ×60 (2 months) × 2/7 (1–3 days/week)/180 (6 months) = 4.8

In this example the total score for the 6 month period is 42.9 (38.1 plus 4.8).

Table 13-4 ASAS recommendations for the approach to collection of NSAID intake for use in clinical trials/epidemiological studies of spondyloarthritis

NSAID intake since the last visit	Yes ☐	No ☐		
NSAID name	Average daily intake	Days with intake	Starting date	Ending date
----------	/___/___/___/ mg	☐ <1 day/week ☐ 1–3 days/week ☐ 3–5 days/week ☐ ≥5 days/week ☐ Everyday	/__/__//__/__//__/__/	/__/__//__/__//__/__/ Ongoing

27. When the name and the dose of the NSAID intake are not available but the number of days with NSAID intake is available, the recommendation is to present the results as the percentage days with at least NSAID intake during a period of time.
28. When the only available data are the NSAID intake at a specific visit, the recommendation is to present the results as the percentage patients taking an NSAID at a specifi c visit.

13.4.2 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)

13.4.3 Bath Ankylosing Spondylitis Functional Index (BASFI)

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

13.4.4 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

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

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

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

13.4.5 Bath Ankylosing Spondylitis Metrology Index (BASMI)

Cervical rotation

Cervical rotation is measured twice with the patient supine on plinth, head in neutral position, forehead horizontal (if necessary, with the head on a pillow or foam block, which must be documented for future reassessments). A goniometer (preferably a gravity goniometer) is placed centrally on the forehead. Patient rotates head as far as possible to the right, keeping shoulders still; ensure no neck flexion or side flexion occurs. The angle between the sagittal plane and the new plane after rotation is recorded. The higher reading of 2 assessments is recorded in degrees. The same procedure is repeated twice for the left side. Record the mean of the higher reading from the right side and the higher reading from the left side.

Tragus to wall distance

Tragus to wall distance is measured twice with the patient's heels and back rested against the wall. The chin should be at usual carrying level and the patient takes maximal effort to touch the head against the wall. The distance between the tragus and the wall is assessed on each side, and an average of the 2 distances from each side is calculated. The procedure is repeated, and the shorter of the 2 average assessments is reported.

Spinal lateral flexion (lumbar lateral flexion)

Patient stands with heels and buttocks touching the wall, knees straight, shoulders back, and hands by the side. The patient bends to the right side as far as possible, without lifting the left foot/heel or flexing the right knee and maintaining a straight posture with heels, buttocks, and shoulders against the wall. The distance from the third fingertip to the floor when patient bends to the side is subtracted from the distance when patient stands upright. The higher of 2 tries is recorded. The maneuver is repeated on the left side. Record the mean of the larger difference from the right side and the larger difference from the left side.

Lumbar flexion (modified Schober index)

Patient is standing erect. Set marks in upright position 5 cm below and 10 cm above lumbosacral junction (spinal section of a line joining the dimples of Venus). Measure the difference between the distance between marks in a standing position (15 cm) versus a forward flexed position when the patient bends forward as far as possible, keeping the knees straight. The procedure is repeated, and the higher difference of the 2 tries is reported.

Maximal intermalleolar distance

Patient is lying down with the legs separated as far as possible with knees straight and toes pointing upwards. Alternatively, the patient stands and separates the legs as far as possible. Distance between medial malleoli is measured, and the higher of the 2 readings is recorded.

Chest expansion

Chest expansion is measured with the patient's hands resting on or behind the head. The measurement is taken at the fourth intercostal level anteriorly. The difference between maximal inspiration and expiration in cm (to the nearest 0.1 cm) is recorded twice, and the higher difference of the 2 tries is reported.

Occiput-to-wall distance

Occiput to wall distance is measured twice with the patient's heels and back rested against the wall. The chin should be at usual carrying level, and the patient takes maximal effort to touch the head against the wall. The distance between the occiput and the wall is assessed, and the shorter of the 2 readings is reported.