NOVARTIS

Clinical Development

AIN457F

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)

Statistical Analysis Plan (SAP)

Author: [redacted], Trial Statistician

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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
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
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
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTRD	Clinical Trial Results Database
DMARD	Disease-modifying antirheumatic drugs
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESR	Erythrocyte sedimentation rate
FAS	Full Analysis Set
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

IVR	Interactive Voice Response
IWR	Interactive Web Response
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
PK	Pharmacokinetics
PFS	Pre-filled syringe
p.o.	per orally
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
SAE	serious adverse event
SAP	Statistical Analysis Plan
s.c.	subcutaneous
SpA	Spondyloarthritides
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
TNFα	tumor necrosis factor alpha
TFLs	Tables, Figures, Listings
VAS	visual analog scale
WHO	World Health Organization

1 Introduction

This document contains details of the statistical methods which will be used in the phase IV clinical trial CAIN457FDE03. This document gives detailed statistical methodology used in the analysis of this study. 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.

Data will be analyzed by statistical software SAS version 9.4 according to the data analysis Section 9 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

1.1 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:

Treatment arms

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% (i.e. 114)of patients are TNFα inhibitor naïve, i.e., no more than 40% (i.e. 76) of patients are TNFα-IR. In theory the percentage of TNFα inhibitor naïve patients could reach 100%, although that is not anticipated.

For primary analysis both the secukinumab treatment arms will be pooled and compared against placebo.

Primary analysis time point

The primary analysis will be performed at 12 weeks.

Planned number of patients

The study is aimed to randomize a total of approximately 190 patients, men or women ≥ 18 years of age who fulfill the modified New York criteria (Explained in the protocol Appendix 3) for AS 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.

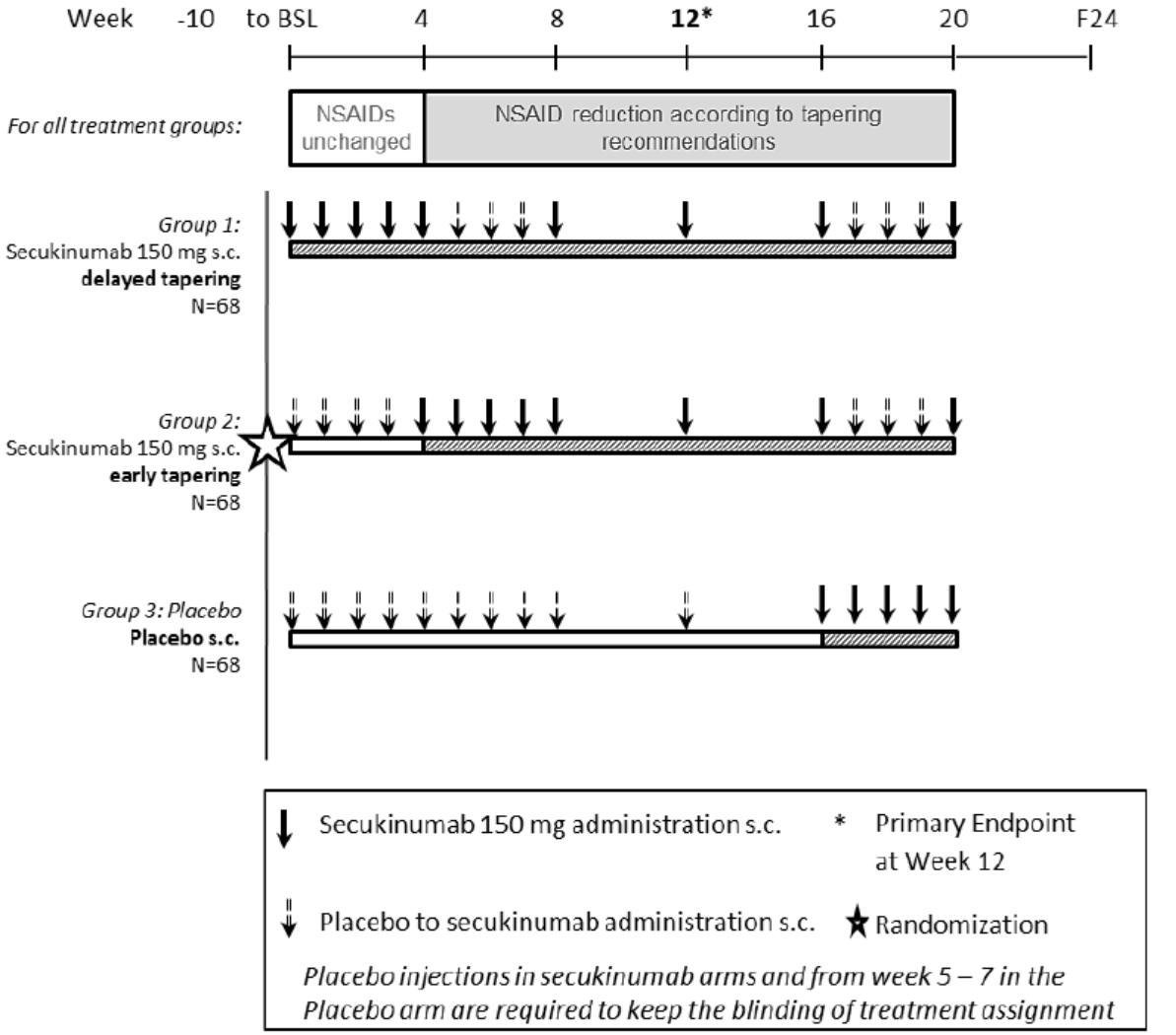
This will be a multi-centric study planned to be conducted across 30-45 sites in Germany.

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

Interim analyses

No interim analysis will be performed for this study.

Figure 1.1-1: Study Design



1.2 Study objectives and endpoints

Table 1.2-1 Objectives and related endpoints

Objective	Endpoint
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.	Proportion of patients fulfilling ASAS20 criteria in the pooled Secukinumab groups (i.e. Secukinumab delayed tapering and Secukinumab early tapering) and placebo regimen at Week 12.
Secondary objective	
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.	Mean change from baseline in ASAS-NSAID score for pooled Secukinumab groups and placebo regimen at Week 12.
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.	Mean change from baseline in total BASDAI score for pooled Secukinumab groups and placebo regimen at Week 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 proportion of patients achieving an ASAS20 response.	Proportion of patients fulfilling ASAS20 criteria for Secukinumab (delayed tapering) versus placebo regimen at week 12
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	Proportion of patients fulfilling ASAS20 criteria for Secukinumab (early tapering) versus placebo regimen at week 12

is superior to placebo based on the proportion of patients achieving an ASAS20 response.	
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.	Proportion of patients fulfilling ASAS20 criteria for Secukinumab (early tapering) versus placebo regimen at week 16
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.	Mean change from baseline in ASAS-NSAID for Secukinumab (delayed tapering) and Placebo at Week 12
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.	Mean change from baseline in ASAS-NSAID for Secukinumab (early tapering) and Placebo at Week 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 the total BASDAI.	Mean change from baseline in total BASDAI score for Secukinumab (delayed tapering) and placebo regimen at Week 12
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.	Mean change from baseline in total BASDAI score for Secukinumab (early tapering) and placebo regimen at Week 12
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.	Mean change from baseline in total BASDAI score for Secukinumab (early tapering) and placebo regimen at Week 16

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.	Mean change from baseline in SF-36 PCS in the pooled Secukinumab groups (i.e. Secukinumab delayed tapering and Secukinumab early tapering) and placebo regimen at Week 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.	Mean change from baseline in SF-36 PCS for Secukinumab (delayed tapering) and placebo regimen at Week 12.
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.	Mean change from baseline in SF-36 PCS for Secukinumab (early tapering) and placebo regimen at Week 12.
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").	Mean change from baseline in total ASAS-NSAID score after 12 weeks of Secukinumab exposure (ASAS-NSAID index at Week 12 for "delayed tapering" vs. Week 16 for "early tapering").
Exploratory objective	
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").	Mean 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").
To evaluate change in patient reported neck, back and hip pain (BASDAI question 2) beginning from Secukinumab treatment on a continuous basis in patients exposed to Secukinumab 150 mg s.c. for 12 weeks vs. placebo.	Mean change in patient reported neck, back and hip pain score (BASDAI question 2) from baseline at Week 12 for secukinumab 150 mg s.c. (delayed tapering) vs. placebo. Mean change in patient reported neck, back and hip pain score from baseline at week 16 for

	secukinumab 150 mg s.c. (early tapering) vs. placebo.
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.	Mean change in patient reported neck, back and hip pain score (BASDAI question 2) from baseline for secukinumab 150 mg s.c. (delayed tapering) vs. placebo from baseline (week 0) to week 12.
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.	Mean change in patient reported neck, back and hip pain score from baseline for secukinumab 150 mg s.c. (early tapering) vs. placebo from week 0 to week 16.
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.	Proportion of patients fullfilling ASAS20 criteria at week 4 for secukinumab 150 mg s.c. (delayed tapering) vs. week 20 in patients switching from placebo after weeks of secukinumab exposure.
To explore the 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 for both secukinumab arms from week 0 to week 12 for secukinumab 150 mg s.c. (delayed tapering) and from week 0 to week 16 for secukinumab 150 mg s.c. (early tapering).
To explore the total ASAS-NSAID [Area Under Curve (AUC)] Score from Week 4 to Week 16 for each treatment arm.	Total ASAS-NSAID [Area Under Curve (AUC)] Score for each treatment arm from Week 4 to Week 16.
To explore the efficacy of secukinumab based on the proportion of patients with no NSAID intake after Secukinumab exposure of 12 weeks.	Proportion of patients with no NSAID intake at week 12 for secukinumab 150 mg s.c. (delayed tapering) and at week 16 for secukinumab 150 mg s.c. (early tapering).
To explore the efficacy of Secukinumab 150 mg s.c. in patients with no NSAID intake at week 12.	Proportion of patients with no NSAID intake at week 12 for each treatment arm.

To explore the efficacy of Secukinumab 150 mg s.c. based on ASAS Health Index after Secukinumab exposure of 12 weeks.	Mean change from Baseline in the ASAS Health Index at week 12 for secukinumab 150 mg s.c. (delayed tapering) and at week 16 for secukinumab 150 mg s.c. (early tapering).
To explore the efficacy of Secukinumab 150 mg s.c. assesed by ASAS Health Index at week 12.	Mean change from Baseline in the ASAS Health Index at week 12.
To explore the Spinal mobility assessed by Bath Ankylosing Spondylitis Metrology Index (BASMI) linear scores.	Mean change from baseline in BASMI linear scores.
To explore the efficacy of Secukinumab 150 mg s.c. in achieving the ASAS40 response over time.	Proportion of patients fulfilling the ASAS40 criteria in each treatment group over time.
To explore the efficacy of Secukinumab 150 mg s.c. in achieving the ASAS20 response over time.	Proportion of patients fulfilling the ASAS20 criteria in each treatment group over time
To explore the efficacy of Secukinumab 150 mg s.c. in achieving the ASAS5/6 response over time.	Proportion of patients fulfilling the ASAS5/6 criteria in each treatment group over time.
To explore the efficacy of Secukinumab 150 mg s.c. assesed by hsCRP.	Mean change from baseline in hsCRP.
To explore the efficacy of Secukinumab 150 mg s.c.assesed by total BASDAI over time.	Mean change from baseline in total BASDAI score in each treatment group over time.
To explore the efficacy of Secukinumab 150 mg s.c.in achieving BASDAI 50 response over time.	Proportion of patients fulfilling BASDAI 50 response criteria in each treatment group over time.
To explore the efficacy of Secukinumab 150 mg s.c.in achieving ASAS partial remission response over time.	Proportion of patients fulfilling ASAS partial remission criteria in each treatment group over time
To explore the efficacy of Secukinumab 150 mg s.c. assesed by 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	Mean change from baseline for each treatment group in ASAS components including: a. Patient global disease activity b. Total spinal pain c. Inflammation (average of BASDAI questions 5 and 6) d. BASFI

d. Bath Ankylosing Spondylitis Functional Index (BASFI	
To evaluate secukinumab 150 mg s.c. versus placebo in achieving an improvement in Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-Reactive Protein (CRP) and ASDAS-Erythrocyte Sedimentation Rate (ESR)	Mean change from baseline in ASDAS-CRP and ASDAS-ESR for each treatment group.
To evaluate secukinumab 150 mg s.c versus placebo with ASDAS inactive disease as defined by ASDAS < 1.3	Proportion of patients with ASDAS inactive disease (i.e ASDAS < 1.3).
To evaluate secukinumab 150 mg s.c versus placebo in ASDAS clinically important improvement (change in ASDAS ≥ 1.1) and major improvement (change in ASDAS ≥ 2.0)	Proportion of patients with ASDAS clinically important improvement (change in ASDAS ≥ 1.1) and major improvement (change in ASDAS ≥ 2.0)
To assess overall tolerability and safety of Secukinumab at reduced NSAID intake.	Overall safety, as measured by frequency and severity of adverse events and changes in laboratory, vital signs and ECG values from baseline.
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.	Proportion of patients for each reason given in the patient diary on why he was not able to taper NSAIDs despite reduced spinal pain.
To compare the secukinumab arms (pooled Group1 and Group2) concerning ASAS20 response criteria after exposition of 12 weeks against placebo at week 12.	Proportion of patients fulfilling ASAS20 criteria in the pooled Secukinumab groups after exposure of 12 weeks (i.e. Secukinumab delayed tapering at week 12 and Secukinumab early tapering at week 16) and placebo regimen at Week 12.
To compare the secukinumab arms (pooled Group1 and Group2) concerning ASAS20 response criteria after exposition of 12 weeks against placebo at week 16.	Proportion of patients fulfilling ASAS20 criteria in the pooled Secukinumab groups after exposure of 12 weeks (i.e. Secukinumab delayed tapering at week 12 and Secukinumab early tapering at week 16) and placebo regimen at Week 16.
To compare the secukinumab arms (pooled Group1 and Group2) concerning ASAS-NSAID score after exposition of 12 weeks against placebo at week 12.	Total ASAS-NSAID score in the pooled Secukinumab groups after exposure of 12 weeks (i.e. Secukinumab delayed tapering at week 12 and Secukinumab early tapering at week 16) and placebo regimen at Week 12.
To compare the secukinumab arms (pooled Group1 and Group2) concerning ASAS-	Total ASAS-NSAID score in the pooled Secukinumab groups after exposure of 12 weeks

NSAID score after exposition of 12 weeks against placebo at week 16.	(i.e. Secukinumab delayed tapering at week 12 and Secukinumab early tapering at week 16) and placebo regimen at Week 16.
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)	

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by Novartis on all patient data after database lock for the respective trial period. It is planned that the data from all centers that participate in this protocol will be used for analysis. Analysis datasets and statistical outputs will be produced using the most recent SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA), and stored in Novartis global programming & statistical environment (GPS).

Continuous data will be summarized by n, mean, standard deviation (SD), median, first and third quartiles, minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %). Summary statistics will also be presented graphically wherever applicable.

If not otherwise specified, p-values and confidence intervals will be two-sided. Unless otherwise stated, the level of significance will be set to 5% (two-sided, family-wise type-I-error).

Decimal places

Decimal places will be as follows:

- p-value: 4 decimal places; if p-value is less than 0.0001, display <0.0001.
- Standard error and standard deviation: data precision + 2 decimal places
- Mean, quartile, percentile and median: data precision + 1 decimal place
- Minimum and maximum: same as data precision
- Percentages: 1 decimal place, 0% will be displayed as 0.0 and 100% will be displayed as 100.0.
- Odds ratios and risk ratios will be displayed with two decimal places.
- Confidence interval (CI): data precision + 2 decimal place.

P-values will not be concatenated with "*" stars in case of significance.

2.1.1 General definitions

Study treatment: Study treatment refers to:

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

Two secukinumab arms will be pooled for the primary analysis and for specified secondary analysis.

Study treatment start and end date: Study treatment start date is defined as the first date when study drug is administered and recorded on the Dose Administration Record (DAR) CRF page. Similarly, study drug end date is defined as the last date when a non-zero dose of study drug is administered and recorded on the DAR CRF page.

Study day: Study day will be calculated as (event date – study drug start date + 1 day) for the safety analysis and (event date – randomization date + 1 day) for the efficacy analysis. For events prior to study drug start date or randomization date (e.g., an adverse event occurred before the start of first dose), study day will be negative and calculated as (event date – study drug start date) and (event date – randomization date) for safety and efficacy analysis respectively.

Screening, baseline and post-baseline definitions

Screening will consist of 2 consecutive visits. During Screening Visit 1, initial assessments will be performed, 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.

However in general, screening refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to the date of first dose of study treatment (for safety analysis) or prior to the randomization date (for efficacy analysis).

For efficacy analyses, baseline is the last assessment, i.e. the last non-missing observation, (including unscheduled visits) obtained before the randomization. All assessments obtained after randomization are considered as post-baseline unless otherwise specified.

For safety analyses, baseline is the last assessment (including unscheduled visits) obtained on or before the first dose of study treatment (i.e. treatment start date). All assessments obtained after the first dose of study treatment are considered as post-baseline unless otherwise specified.

In general, a baseline value refers to the last measurement made prior to administration of the first dose of study treatment. However, LAB assessments if no pre-treatment value exists, values obtained after first dose of treatment can be used as baseline only if it was collected on the same day as first dose.

Study completion: 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).

Study periods: The study has 3 periods: a screening period consisting of two visits (screening visit 1 and screening visit 2), a treatment period consisting of treatment period 1, treatment period 2, and follow up period of 4 weeks.

Treatment Period: There are 2 treatment periods for this study defined as:

Treatment Period 1 is defined as a placebo-controlled, double-blind treatment period starting from baseline till Week 16 pre-dose.

Treatment Period 2 is a double-blinded treatment period starting from Week 16 post-dose till Week 20.

Lost to follow up: The patients whose study completion status is unclear because they fail to appear for study visits without stating an intention to withdraw. A patient should not be formally considered lost to follow-up until his/her scheduled end of treatment visit would have occurred.

2.1.2 Visit windows

Analysis visit windows will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are protocol defined scheduled visits around which analysis visit windows were created to cover the complete range of days within the study. When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the *Week 4* visit of a subject is delayed and occurs on Day 46 instead of on Day 29, say, it will be re-aligned to visit window *Week 8*. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

Of note, subjects are allowed to have gaps in visits. All data collected will be displayed in listings.

Table 2-1 Analysis visit windows

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	BSL	1	Up to Day 1*
Week 1	1	8	Day 2-11
Week 2	2	15	Day 12-18
Week 3	3	22	Day 19-25
Week 4	4	29	Day 26-32
Week 5	5	36	Day 33-39
Week 6	6	43	Day 40-46
Week 7	7	50	Day 47-53
Week 8	8	57	Day 54-71
Week 12	12	85	Day 72-99
Week 16	16	113	Day 100-116
Week 17	17	120	Day 117-123
Week 18	18	127	Day 124-130
Week 19	19	134	Day 131-137
Week 20	20	141	Day 138-165

* Baseline measurement before the first drug administration for safety assessments and before the randomization for efficacy assessments. For efficacy visit windows, refer to date of randomization.

For parameters, which are not collected at every visit, visit windows defined in Table 2-1 will be combined. For example, if a parameter is measured at Week 12 and Week 20 only, Week 12 visit window will extend from Day 2 to Day 99 (combining Week 1 to Week 12 visit windows), Week 24 will extend from Day 100 to Day 165 (combining Week 16 to Week 20).

The mapping described above applies to all visits (not just scheduled visits). Repeat and/or unscheduled visits (which will be numbered in the database according to new NCDS standards) will be mapped for analysis purposes in the same way as scheduled visits. This leaves the possibility, then, for multiple measurements within an analysis window. The following conventions will be used to determine the appropriate measurement to be summarized in the event of multiple measurements within a visit window.

Table 2-2 Rules for flagging values

Timing of measurement	Type of data	Rule
Baseline	All data	The last measurement made prior to administration of the first dose of study treatment – note this may include measurements taken on the day of randomization (e.g. lab). If a patient did not receive any dose of study treatment then the randomization date will be used.

Timing of measurement	Type of data	Rule
Post-baseline efficacy	All data	• For visits without switch of treatment in the window, the measurement closest to the target will be used. In the event two measurements are taken equally apart (e.g. 1 before target date and 1 after) the first one will be used. • For visits during which the patient switches from placebo to AIN the following will be done: o If the analysis visit window is <= week 16, then: ▪ If available, the closest measurement to the target date which is ON or BEFORE the switch date will be used (i.e. the closest measurement to target which is on placebo). ▪ If there are no data on or before the switch then the closest measurement to the target date after the switch will be used. o If the analysis visit window is > week 16, then ▪ If available, the closest measurement to the target date which is AFTER the switch date will be used (i.e. the closest measurement to target which is on AIN). ▪ If there are no data AFTER the switch then the closest measurement to the target date before the switch will be used.
Post-baseline safety	Summary visit information (e.g. lab, ECG, etc.)	• For visits without switch of treatment in the window, the measurement closest to the target will be used. In the event two measurements are taken equally apart (e.g. 1 before target date and 1 after) the first one will be used. • For visits during which the patient switches from placebo to AIN the following will be done: o If the analysis visit window is <= week 16, then: ▪ If available, the closest measurement to the target date which is ON or BEFORE the switch date will be used (i.e. the closest measurement to target which is on placebo). ▪ If there are no data on or before the switch then the closest measurement to the target date after the switch will be used. o If the analysis visit window is > week 16, then ▪ If available, the closest measurement to the target date which is AFTER the switch date will be used (i.e. the closest measurement to target which is on AIN). ▪ If there are no data AFTER the switch then the closest measurement to the target date before the switch will be used.

Timing of measurement	Type of data	Rule
Post-baseline safety	Notable abnormalities (e.g. lab)	The most extreme measurement in the window will be used. Note this means a patient can have a notably high and notably low measurement within a window.

2.2 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.

2.2.1 Subgroup of interest

Summary of the primary variable will also be presented by the below subgroups:

- ASAS-NSAID
  - Lower user groups (baseline score <75)
  - Higher user group (baseline score >=75)
- Gender
  - Male
  - Female

2.3 Patient disposition, demographics and other baseline characteristics

All data about disposition, patient demographics and baseline characteristics, including derived variables, will be summarized by treatment groups (secukinumab delayed tapering, secukinumab early tapering and placebo) and overall with summary descriptive statistics for all the patients in Randomized set. Continuous data will be summarized by n, mean, standard deviation, median, first and third quartiles, minimum and maximum. Categorical data will be presented by absolute frequency and percentages.

The number of the analysis populations will be described and the reasons for excluding a patient from any particular population will be provided with the number of protocol violators for each criterion. The difference between treatment groups with respect to protocol deviations and reasons for dropout will be examined by summarizing the protocol deviations by treatment groups and overall on the all patients.

2.3.1 Patient disposition

Summary of disposition for screening phase and study completion phase will be presented separately.

For screening phase disposition, the number and percentage of patients screened, completed screening phase, screen failures along with the reasons for screen failures as captured in CRF and randomized for all screened patients.

For study completion phase disposition, the number and percentage of patients completed the study and discontinued from the study will be summarized by treatment groups and overall with reasons for discontinuation for all patients in Randomized set.

Listing for patients whether they completed or discontinued from the study at screening phase and study completion phase disposition will be provided separately with the date of discontinuation and primary reason for discontinuation.Listing for protocol deviations will be presented seperately for all the patients in Full Analysis Set.

2.3.2 Patient demographic and other baseline characteristics

The following demographic and baseline variables, if collected, will be summarized based on randomized set:

Demographic variables:

Continuous variables:

- Age (years)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2) will be calculate as (body weight in kilograms) / $(\text{height in meters})^2$
- Smoking usage (Pack years)

Categorical variables:

- Age categories (<65 years, >=65 and <75 years, 75 years and older)
- Gender (Male, Female)
- Race (Caucasian, Black, Asian, Other)
- Smoking status (Never, current, former)
- Source of patient referral
    - Physician's own practice
    - Physician referral
    - Print advertisement
    - Newsletter/educational material
    - Novartis internet site

- Non-Novartis internet site
- Clinical trial registry
- Other

Baseline disease characteristics variables:

Continuous variables:

- Duration of disease (months)
- Dose of methotrexate or other DMARD at randomization
- Patient's global assessment of disease activity
- Patient's assessment of back pain intensity
- BASMI
- BASDAI
- BASFI
- hsCRP
- ASDAS-CRP
- ESR (Erythrocyte Sedimentation Rate)
- ASDAS-ESR
- Number of prior biologic AS therapies
- ASAS Health Index
- SF-36 Physical Component Score
- SF-36 Mental Component Score

Categorical variables:

- TNF- alpha inhibitor status
  - Naïve
  - Inadequate responder
- History of Extra-Axial Involvement
  - Uveitis
  - Psoariasis
  - Inflammatory bowel disease
  - Dactylitis
  - Enthesitis
  - Peripheral arthritis

- HLA-B27 status
  - Positive
  - Negative
- hsCRP category
  - hsCRP-level ≤ 5 mg/L
  - hsCRP-level > 5 mg/L
- ASDAS-CRP disease state
  - Inactive disease (ASDAS < 1.3)
  - Low disease activity (ASDAS>= 1.3 and ASDAS< 2.1)
  - High disease activity (ASDAS >= 2.1 and ASDAS<=3.5)
  - Very high disease activi ty (ASDAS > 3.5)
- NSAIDs or selective COX-2-inhibitors usage
- Corticoisteroids (prednisone or equivalent) usage
  - ≤7.5 mg/day
  - >7.5 mg/day
- PPD test
  - Negative
  - Positive
- SF-36
  - Physical Component Score
  - Mental Component Score
- Enviromental factors related to ASAS HI

Medical history

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

Summaries for cardiovascular medical history and ankylosing spondylitis medical history will be provided as well, if collected.

Smoking history will be summarized by treatment group.

Unless otherwise specified, analyses will be based on the randomized set.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The summaries by treatment will be performed by the randomized treatment or treatment sequence.

- Randomized treatment:
  - AIN457 150mg (delayed tapering)
  - AIN457 150mg (early tapering)
  - Placebo
- Treatment sequence:
  - AIN457 150mg (delayed tapering)
  - AIN457 150mg (early tapering)
  - Placebo-AIN457 150mg

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

Duration of exposure

Duration of exposure will be defined as the time from first dose of study treatment to the time of end of treatment period. For patients who discontinue, this will be the patient's last visit in the treatment period.

The exposure to investigational drug (number of doses) and duration of exposure to study treatment will be summarized by treatment group and overall.

In addition, the number and percentage of patients with cumulative exposure levels (e.g. any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, ≥ 5 weeks, ≥ 6 weeks, ≥ 7 weeks, ≥ 8 weeks, ≥ 12 weeks, ≥ 16 weeks, ≥ 17 weeks, ≥ 18 weeks, ≥ 19 weeks, ≥ 20 weeks) will be presented.

Compliance

Compliance will be calculated based on documented study treatment administration details and displayed by treatment group and overall. Total actual dose will be compared with the total dose patients should take as per protocol and derived compliance will be summarized.

Total actual dose will be derived as

Total actual dose = Actual amount of dose of Secukinumab 150 mg upto week 20 × Frequency of dose upto week 20.

The treatment compliance will be calculated by Statistical Programming team as

$$\text{Treatment compliance (\%)} = \frac{\text{the actual number of injections received by a patient}}{\text{the scheduled number of injections}} \times 100.$$

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

Drug interruptions

The number and percentage of patients with permanent study drug interruptions and the reasons that led to the interruption will be summarized by treatment group and overall on the Safety set.

2.4.2 Prior, concomitant and post therapies

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.

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

Safety set will be used for the above analysis.

2.5 Analysis of the primary objective

The primary objective is 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.

Primary variable

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

2.5.1 Estimand of primary variable

Proportion of patients fulfilling ASAS20 criteria in the pooled Secukinumab groups and Placebo regimen at Week 12. The analysis of the primary endpoint will be based on the FAS population. The analysis of the primary variable will be based on the following estimand:

- Population: patients in full analysis set
- 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) of ASAS20 response for secukinumab pooled groups and placebo

2.5.2 Statistical hypothesis, model, and method of analysis of primary estimand

The statistical hypothesis for ASAS20 being tested is

$$H_o : p_1 = p_0$$

v/s

$$H_1 : p_1 \neq p_0$$

where p0 denotes the proportion of ASAS20 responders in the placebo and p1 denotes the proportion of ASAS20 responders in the pooled Secukinumab groups at week 12.

Secukinumab groups will be pooled using their measurements at week 12.

The primary analysis will be performed using 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 the Secukinumab (pooled) groups to placebo.

2.5.3 Handling of missing values/censoring/discontinuations

Missing data for ASAS20 response for data up to Week 20 will be handled as follows:

Non-responder imputation:

1. Patients who drop out of the trial for any reason will be considered non-responders from the time they drop out through Week 20.

2. Patients who do not have the required data to compute ASAS20 response 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.

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.

2.5.4 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

These analyes will not be included in the CSR.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

Refer to Table 1.2-1 of Section 1 for the list of secondary objectives.

2.7.1 Secondary endpoints

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

Please refer to the main definition section.

2.7.2 Statistical hypothesis, model, and method of analysis

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 objectives:

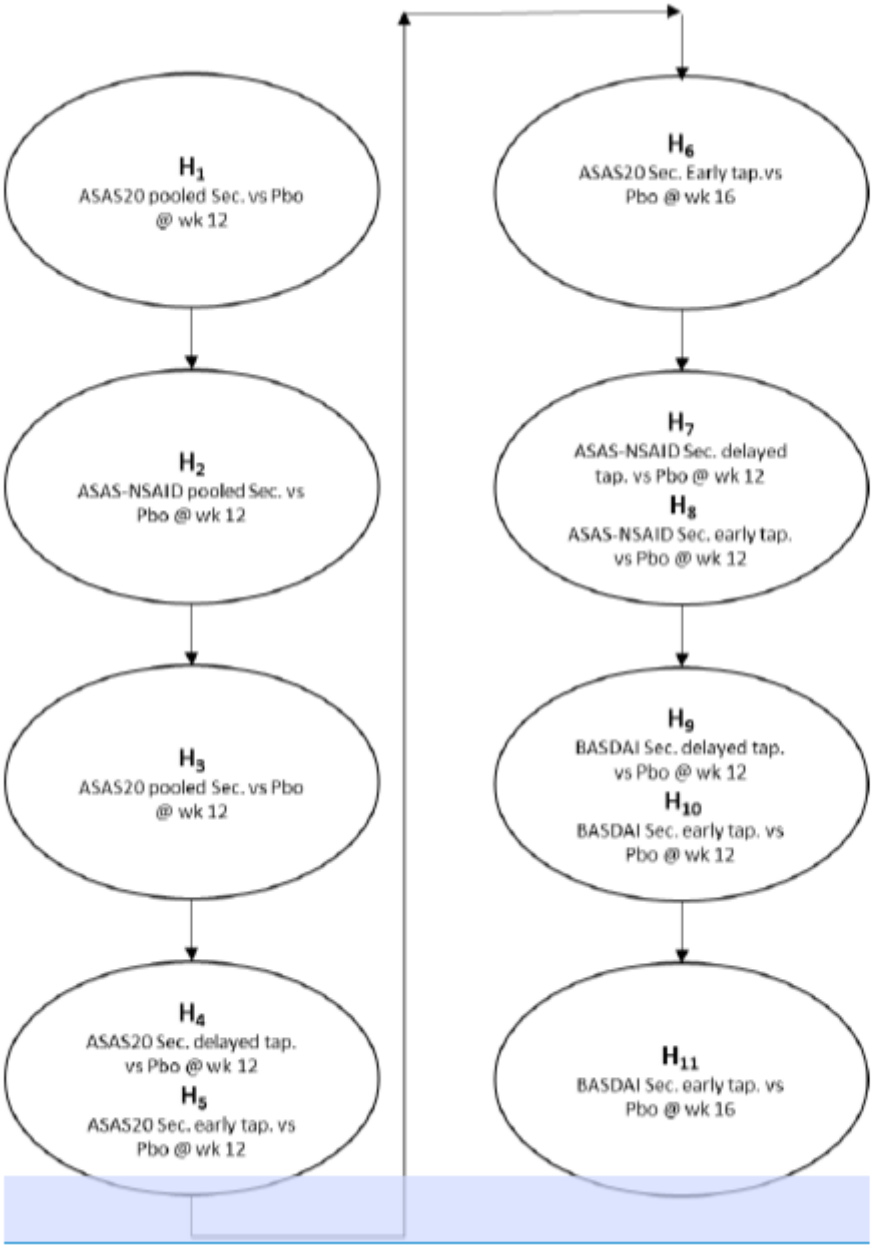
- H_1: Secukinumab 150 mg s.c. (pooled secukinumab groups) is not different to placebo regimen with respect to signs and symptoms (ASAS20 response) at Week 12.

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.

Analysis of secondary efficacy variables

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.

Refer to Appendix section 5.1 for calculation of ASAS20.

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. Initially 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.

Refer to Appendix section 5.1 for calculation of ASAS-NSAID scores.

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. The adjusted (LS) mean difference will be calculated as a point estimate together with the corresponding 95% confidence interval and p-value.

Refer to Appendix section 5.1 for calculation of BASDAI scores.

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.

2.7.3 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 secondary analysis will use the non-responder imputation only.

2.8 Safety analyses

For all safety analyses, the Safety set will be used.

Summaries may be performed separately for different treatment periods.

The analyses of the follow-up period will be limited to summaries for treatment-emergent

adverse events, and serious adverse events.

Safety analyses will be performed on treatment received or actual treatment as described below:

The actual treatment or treatment received for summaries of safety data will differ to the treatment assigned at randomization only if a subject received the wrong treatment during the entire study.

For those patients who received not the treatment randomized, i.e. who received erroneously the wrong treatment at least once, an additional AE listing will be prepared displaying which events occurred after the treatment errors and also the relationship with study drug.

2.8.1 Adverse events (AEs)

The crude incidence of treatment emergent adverse events (i.e. 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, and events until 30 days for AE and SAE after last dose of study treatment) will be summarized by primary system organ class and preferred term.

The summaries will be presented separtely by study periods i.e. week 1-16 and after week 16.

In addition, exposure time-adjusted incidence rates including 95% confidence intervals will be provided for the entire treatment period to adjust for differences in exposure. A graphical display of the crude rates and exposure-adjusted incidence rates will be presented for all AEs and serious AEs by system organ classA graphical display of relative frequencies within system organ classes and relative risks, as appropriate, will be presented.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having at least one AE, having an AE in each primary system organ class and having each individual AE (preferred term).

The most common adverse events reported (>1 % in any group for each preferred term in the

SOC-PT table or > 1 % in any group) will be presented in descending frequency according to its incidence in total secukinumab group (combining all secukinumab treatment groups) starting from the most common event.

Summaries (crude incidences only) will also be presented for AEs by severity and for study treatment related AEs.If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. 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.

Separate summaries will be provided for

- adverse events suspected to be related to study drug by the investigator
- deaths
- adverse events leading to discontinuation
- adverse events leading to temporary dose interruption.

The MedDRA version used for reporting the study will be described in a footnote.

Follow-up period summaries will be done for all patients in follow-up.

A listing of non-treatment emergent adverse events will be done. These adverse events

occurred before the first dose of the study treatment.

Algorithms for date imputations will be provided in Programming Specifications.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE

2.8.1.1 Serious adverse event

Serious adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having at least one SAE, having an SAE in each primary system organ class and having each individual AE (preferred term). For SAEs occurred during screening a listing will be prepared for all patients screened including screening failures.

2.8.1.2 Adverse events of special interest (AESIs)

- The following events will be considered as adverse events of special interest:
- Infection and infestations
- Mood disorder/ depression
- Inflammatory bowel disease

The crude rates and exposure-adjusted incidence rates for AESIs will be summarized.

Important note: For the evaluation of AESIs risks primary and secondary system organ classes of the MedDRA dictionary will be considered.

Specific groupings of AESI will be considered and the number of patients with at least one event in each grouping will be reported. Such groups consist of adverse events for which there is a specific clinical interest in connection with secukinumab or adverse events, which are similar in nature (although not identical). Note that certain adverse events may be reported within multiple groupings.

All AESI groupings are defined through the use of PT, high level terms (HLT), SOC, SMQ , NMQ or through a combination of these components.

The AESI search table will be used to map reported adverse events to the notable adverse events groupings. The list of adverse events of special interest may be updated during the course of the trial based on accumulating safety data. Therefore, the clinical study report will list the AE groupings used and provide a listing of the corresponding AESI search table.

2.8.2 Deaths

Deaths will be separately summarized by treatment group and overall on the safety set. Also, listing of deaths will be provided on safety set.

2.8.3 Laboratory data

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

In addition to the individual laboratory parameters the ratios “total cholesterol / HDL” and “apolipoprotein B / apolipoprotein A1” will be derived and summarized.

Hematology

The following hematology variables will be analyzed :

- Hemoglobin,
- hematocrit,
- red blood cell count,
- white blood cell count with differential counts, and
- platelet count.

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.

For urinalysis, frequency tables will be presented.

Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test and treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline value – baseline value

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

In addition, shift tables will be provided for all parameters to compare a patient's baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high The shifts to the most extreme laboratory test value within a treatment period will be presented(including category "high and low"). These summaries will be presented by laboratory test and treatment group.

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in Table 2.8-1: hemoglobin, platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glucose, cholesterol, triglycerides (TG).

These summaries will be split into hematology and chemistry for study level reports and the pooled summary of clinical safety.

Table 2.8-1 CTCAE grades for laboratory parameters to be analyzed

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	<LLN – 100 g/L	<100 – 80 g/L	<80 g/L	
Platelet count decreased	<LLN – 75.0 x10e9 /L	<75.0 - 50.0 x10e9 /L	<50.0 – 25.0 x10e9 /L	<25.0 x 10e9 /L
White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L
Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Creatinine increased*	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 xULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
TBL increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALT increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALP increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Glucose increased (Hyperglycemia)	>ULN - 8.9 mmol/L	>8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L	>27.8 mmol/L
Glucose decreased (Hypoglycemia)	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L

Cholesterol high	>ULN - 7.75 mmol/L	>7.75 - 10.34 mmol/L	>10.34 - 12.92 mmol/L	>12.92 mmol/L
Hypertriglyceridemia	1.71 - 3.42 mmol/L	>3.42 - 5.7mmol/L	>5.7 - 11.4 mmol/L	>11.4 mmol/L

*Note: for "creatinine increased" the baseline criteria do not apply

Shift tables will be presented comparing baseline laboratory result (CTCAE grade) with the worst results (expressed in CTCAE grade) during the treatment phase (either initial or entire) analyzed. Of note, baseline will be defined as last assessment prior to first dosing in initial treatment phase. Patients with abnormal laboratory values will be listed and values outside the normal ranges will be flagged.

Summaries for newly occurring or worsening clinically notable lipid abnormalities will also be provided cumulatively for each of the following parameters and categories:

- HDL:
  - <=LLN
  - <0.8 x LLN
- LDL, cholesterol, triglycerides:
  - >=ULN
  - >1.5 x ULN
  - >2.5 x ULN

Newly occurring or worsening liver enzyme abnormalities will also be summarized based on the event criteria given in Table 2.8-3 below:

Table 2.8-2 Liver-related events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN, >20xULN
AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
ALT or AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
TBL	>1.5xULN, >2xULN, >3xULN,
ALP	>2xULN, >3xULN. >5xULN
ALT or AST & TBL	ALT or AST>3xULN & TBL >2xULN; ALT or AST >5xULN & TBL >2xULN; ALT or AST >8xULN & TBL >2xULN; ALT or AST >10xULN & TBL >2xULN
ALP & TBL	ALP >3xULN & TBL >2xULN ALP >5xULN & TBL >2xULN
ALT or AST & TBL & ALP	ALT or AST>3xULN & TBL >2xULN & ALP <2xULN (Hy's Law) Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of pure hepatocellular injury. This does not mean that cases of ALT or AST >3xULN & TBL >2xULN & ALP ≥2xULN may not result in severe DILI.

Notes:
In studies which enroll patients with pre-existing liver disease, baseline LFT may be increased above ULN; in such a case it is meaningful to add the condition "and worse than baseline" to the abnormality

Criteria

For a combined criterion to be fulfilled, all conditions have to be fulfilled on the same visit.

The criteria are not mutually exclusive, e.g. a subject with ALT = 6.42xULN is counted for ALT >3xULN and ALT>5x ULN.

Individual subject data listings will be provided for patients with abnormal laboratory data.

Data of patients with newly occurring or worsening liver enzyme abnormalities will be listed in an additional listing.

HLA-B27

Human Leukocyte Antigen-B27 (HLA-B27) will be summarized at baseline and also listing will be provided.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Not applicable.

2.8.4.2 Vital signs

Analysis in vital signs measurement 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 (sitting SBP, DBP (mmHg) and pulse(beats/min))) and treatment group. Change from baseline will only be summarized for patients with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value.

2.8.4.3 Urine pregnancy test

Descriptive summaries using number and percentages and listings will be provided for urine pregnancy results (positive, negative) by visit for each treatment period.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

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

ASAS Health Index and enviromental factors related to ASAS HI

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 health index is a linear composite measure and contains 17 items (dichotomous response option: "I agree" and "I do not agree").

Each statement on the ASAS Health Index is given a score of 1 = I agree OR 0 = I do not agree. All item scores are summed up to give a total score that ranges from 0 (good functioning) to 17 (poor functioning).

Summary of ASAS Health Index and environmental factors related to ASAS HI scores will be presented.

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.

Frequency of BASFI response along with the summary of BASFI score will be presented.

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.

For analysis of BASDAI refer to section 2.7.2

SF-36 Health Survey

The Short Form Health Survey (SF-36) is a widely used and extensively studied instrument to measure health-related quality of life among healthy subjects 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. Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed. 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.

For analysis of SF-36 refer to section 2.7.2

2.12 Biomarkers

Not applicable.

2.13 Other Exploratory analyses

All the exploratory efficacy evaluation will be performed on FAS population. Refer to Table 1.2-1 of Section 1 for the list of exploratory endpoints.

The following exploratory efficacy variables will be summarized on the FAS for all applicable analysis visits unless otherwise specified.

1. Total ASAS-NSAID [Area Under Curve (AUC)] Score from treatment start with Secukinumab to a Secukinumab exposure of 12 weeks.
2. Total ASAS-NSAID [Area Under Curve (AUC)] Score From Week 4 to Week 16
3. Proportion of patients with no NSAID intake after Secukinumab exposure of 12 weeks
4. Proportion of patients with no NSAID intake at week 12.
5. Change from Baseline in the ASAS Health Index after Secukinumab exposure of 12 weeks
6. Change from Baseline in the ASAS Health Index at week 12
7. Change from baseline in BASMI
8. ASAS40 response
9. ASAS20 response
10. ASAS5/6 response
11. Change from baseline in hsCRP
12. Change from baseline in total BASDAI
13. BASDAI 50 response

14. ASAS partial remission
15. Change from baseline in ASAS components including:

    Patient global disease activity

    Total spinal pain

    Inflammation (average of BASDAI questions 5 and 6)

    BASFI
16. Change from baseline in ASDAS-CRP and ASDAS-ESR
17. ASDAS inactive disease as defined by ASDAS < 1.3
18. ASDAS clinically important improvement (change in ASDAS ≥ 1.1) and major improvement (change in ASDAS ≥ 2.0)
19. Reasons given in the patient diary on why he was not able to taper NSAIDs despite reduced spinal pain

All endpoints relating to exploratory objectives will be summarized descriptively. Summary statistics will include absolute frequencies and percentages for the categorical variables and the number of patients (n), minimum, mean, median and maximum for continuous variables. Change from baseline will also be presented for some exploratory variables based on the the endpoints mentioned in section 1 Table 1.2-1. Graphical representation will also be performed if required.

The following exploratory endpoints will also be summarized categorically as absolute and relative frequencies (proportions, %).

- Proportion of patients fullfilling ASAS20 criteria at week 4 for secukinumab 150 mg s.c. (delayed tapering) vs. week 20 in patients switching from placebo after weeks of secukinumab exposure.
- Proportion of patients with no NSAID intake at week 12 for secukinumab 150 mg s.c. (delayed tapering) and at week 16 for secukinumab 150 mg s.c. (early tapering).
- Proportion of patients with no NSAID intake at week 12 for each treatment arm.
- Proportion of patients fulfilling the ASAS40 criteria in each treatment group over time.
- Proportion of patients fulfilling the ASAS20 criteria in each treatment group over time.
- Proportion of patients fulfilling the ASAS5/6 criteria in each treatment group over time.
- Proportion of patients fulfilling BASDAI 50 response criteria in each treatment group over time.
- Proportion of patients fulfilling ASAS partial remission criteria in each treatment group over time.
- Proportion of patients with ASDAS inactive disease (i.e ASDAS < 1.3).
- Proportion of patients with ASDAS clinically important improvement (change in ASDAS ≥ 1.1) and major improvement (change in ASDAS ≥ 2.0).

- Proportion of patients for each reason given in the patient diary on why he was not able to taper NSAIDs despite reduced spinal pain.
- Proportion of patients fulfilling ASAS20 criteria in the pooled Secukinumab groups after exposure of 12 weeks (i.e. Secukinumab delayed tapering at week 12 and Secukinumab early tapering at week 16) and placebo regimen at Week 12.
- Proportion of patients fulfilling ASAS20 criteria in the pooled Secukinumab groups after exposure of 12 weeks (i.e. Secukinumab delayed tapering at week 12 and Secukinumab early tapering at week 16) and placebo regimen at Week 16.
- Total ASAS-NSAID score in the pooled Secukinumab groups after exposure of 12 weeks (i.e. Secukinumab delayed tapering at week 12 and Secukinumab early tapering at week 16) and placebo regimen at Week 12.
- Total ASAS-NSAID score in the pooled Secukinumab groups after exposure of 12 weeks (i.e. Secukinumab delayed tapering at week 12 and Secukinumab early tapering at week 16) and placebo regimen at Week 16.

Total BASDAI, BASDAI question 1 and question 2 and ASAS-NSAID score (each in Y-axis) compared to time (X-axis) will be presented graphically.

2.14 Interim analysis

No interim analysis is planned for this study.

3 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 the 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 190) 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.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

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

5.1.2 AE date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSTD)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	NC Uncertain	NC Uncertain	NC Uncertain	NC Uncertain
YYYY < TRTY	(D) Before Treatment Start	(C) Before Treatment Start	(C) Before Treatment Start	(C) Before Treatment Start
YYYY = TRTY	(B) Uncertain	(C) Before Treatment Start	(A) Uncertain	(A) After Treatment Start
YYYY > TRTY	(E) After Treatment Start	(A) After Treatment Start	(A) After Treatment Start	(A) After Treatment Start

The following table is the legend to the logic matrix.

If AE end date is complete and AE end date < Treatment start date or AE end date is partial and AE imputed end date < Treatment start date, then AE start reference = min (informed consent date, earliest visit date from SV) Else if AE end date is partial,AE end date > = Treatment start date or AE is ongoing , then AE start reference = treatment start date.

Relationship	Time imputation
Before AE start reference	Partial date indicates AE start date prior to AE start reference
After AE start reference	Partial date indicates AE start date after AE start reference

Relationship		Time imputation
Uncertain	Partial date insufficient to determine relationship of AE start date to AE start reference	
Imputation Calculation		
NC/Blank	No convention	
(A)	MAX(01MONYYYY, AE start reference+1 day)	
(B)	AE start reference+1	
(C)	15MONYYYY	
(D)	01JULYYYY	
(E)	01JANYYYY	
Complete date	No date imputation	If time is cuptured for the study Case1 : if AE start date is not equal to AE start reference then do the following: If minutes missing then AESTMF = M and time is imputed to hh:00 If minutes missing then AESTMF = H and time is imputed to 00:00 Case2: if AE start date = AE start reference then AESTMF = H and time is imputed to treatment start time + 1 hour

Adverse Event End Date Imputation

Imputed date = date part of original date, if complete date

Imputed date = min (completion/discontinuation visit date, DEC 31, date of death), if month is missing

Imputed date = min (completion/discontinuation visit date, last day of the month, date of death), if day is missing

Adverse Event End Time Imputation

If the AE end date is complete and time is captured in the study then:

Case 1. if AE end date is not equal to Treatment end date, then do the following:

if minutes missing then time is imputed to hh:00 if time missing then time is imputed to 00:00

Case 2: if AE end date = Treatment end date then time is imputed to treatment end time

If the AE end date is partial then end time is imputed to 00:00.

Imputed Date Flag

If year of the imputed date is not equal to YYYY then date flag = Y

else if month of the imputed date is not equal to MON then date flag = M

else if day of the imputed date is not equal to day of original date then date_flag = D

else date flag = null

Imputed Time Flag

If hours of the imputed time is not equal to hours of original time then time flag = H

else if minutes of the imputed time is not equal to minutes of original time then time flag = M

else time flag = null.

5.1.3 Concomitant medication date imputation

This algorithm is used when *event* is the partial start date of the concomitant medication.

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial CM Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSDT)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	**(C2)** Uncertain	**(C1)** Uncertain	**(C1)** Uncertain	**(C1)** Uncertain
YYYY < TRTY	**(D)** Before Treatment Start	**(A)** Before Treatment Start	**(A)** Before Treatment Start	**(A)** Before Treatment Start
YYYY = TRTY	**(C2)** Uncertain	**(A)** Before Treatment Start	**(C1)** Uncertain	**(B)** After Treatment Start
YYYY > TRTY	**(E)** After Treatment Start	**(B)** After Treatment Start	**(B)** After Treatment Start	**(B)** After Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Treatment Start	Partial date indicates CMD start date **prior** to Treatment Start Date
After Treatment Start	Partial date indicates CMD start date **after** Treatment Start Date
Uncertain	Partial date **insufficient to determine** relationship of CMD start date relative to Treatment Start Date
Imputation Calculation	
(A)	15MONYYYY
(B)	01MONYYYY
(C1 or C2)	IF relative reference start = before treatment star THEN TRTSDT-1 ELSE IF relative reference start = ' ' THEN TRTSDT+1
(D)	01JULYYYY

(E)	01JANYYYY

Concomitant Medication End Date Imputation

If not ongoing then -

Imputed date = date part of CMENDTC, if complete date

Imputed date = min(completion/discontinuation visit date, DEC 31) , if month is missing, (C2, D, E)

Imputed date = min(completion/discontinuation visit date, last day of the Month) , if day is missing. (A, B, C1)

Concomitant Medication Date Flag

If not a complete date then

Y - If year of the imputed date is not equal to YYYY else M – If month of the imputed date is not equal to MON else D.

5.1.3.1 Prior therapies date imputation

Not applicable.

5.1.3.2 Post therapies date imputation

Not applicable.

5.1.4 Medical History date of diagnosis imputation

Completely missing dates will not be imputed. Partial dates of diagnosis will be compared to the treatment start date.

- If DIAG year < study treatment start date year and DIAG month is missing, the imputed DIAG date is set to the mid-year point (01JULYYYY)
- Else if DIAG month is not missing, the imputed DIAG date is set to the mid-month point (15MONYYYY)

If DIAG year = study treatment start date year and (DIAG month is missing OR DIAG month is equal to study treatment start month), the imputed DIAG date is set to one day before study treatment start date.

5.2 AEs coding/grading

Not applicable.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

Covariance (ANCOVA) model:

Endpoints with continuous data type expected to be normally distributed will be analyzed using an analysis of covariance (ANCOVA) model with treatment and baseline stratification factors, baseline weight and baseline value and as covariates. Confidence intervals for the difference between each dose of secukinumab and placebo will be calculated.

SAS code for ANCOVA:

```
proc mixed data=aaa;
class TRT STRATA;
model response = TRT STRATA WEIGHT BASE / s;
lsmeans TRT / diff;
run;
```

In addition, key secondary variables measured at all post baseline visits up to Week 20 will be analyzed using longitudinal mixed effects ANCOVA model with treatment, baseline stratification factor and analysis visit as factors; and weight, baseline value, treatment by visit and baseline by visit interactions as covariates. 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 at the appropriate analysis visits.

SAS code for mixed model:

```
proc mixed data=aaa;
class TRT USUBJID AVISITN STRATA;
model CHG=TRT STRATA AVISITN WEIGHT BASE TRT*AVISITN BASE*AVISITN
/ s ddfm=kr;
lsmeans TRT*AVISITN / diff cl;
repeated AVISITN / type=un subject=USUBJID;
Run;
```

In case the MMRM model does not converge the following sequential steps will be used:

1. change ddfm=kr to ddfm=bw. If still no convergence, perform step 2.

2. change type=un to type=cs. If still no convergence, perform step 3.

3. remove covariates of the model based on the scenario.

Logistic regression model:

Certain binary outcome variables, e.g. response outcomes, will be evaluated using a logistic regression model with treatment regimen, weight, stratum if applicable. Odds ratios will be computed for comparisons of AIN457 regimens versus control(s) utilizing the logistic regression model fitted.

SAS code for logistic regression:

```
Proc logistic data=aaa;
Class TRT STRATA / param=glm;
Model AVAL = TRT WEIGHT STRATA;
Lsmeans TRT / diff cl exp;
Ods output diffs=lsm_diff;
Run;
```

In cases where separation is a concern for the primary endpoint at Week 12, e.g. 0% or 100% response in one treatment (sub)group, an exact logistic regression model will be applied to all visits. To ensure convergence, this model will not include any continuous covariates.

```
Proc logistic data=aaa exactonly;
Class TRT STRATA / param=glm;
Model AVAL = TRT STRATA;
Exact TRT / estimate=both;
Ods output exactoddsratio=exactoddsratio;
Run;
```

When exact logistic regression is unable to be implemented (due to computational complexity as the procedure can lead to extremely long run times), then Fisher's exact test will be applied for each AIN457 group versus placebo comparison. In this case, no odds ratios or confidence intervals can be estimated due to 0% response in one of thegroups, but p-values may be calculated.

```
Proc freq data=aaa;
Table TRT * AVAL / fisher;
Where TRT in ( "AIN457 xx mg"  "Placebo" );
Run;
```

5.5 Score derivations and response criteria

5.5.1 Assessment of Spondyloarthritis International Society (ASAS)

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

1. Patient's global assessment of disease activity measured on a VAS scale.

2. Patient's assessment of IBP, represented by either total or nocturnal pain scores, both measured on a VAS scale. For ASAS response analysis, the total back pain score will be used.

3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS scale.

4. Morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI regarding morning stiffness as measured by VAS scale.

Additional assessment domains:

5. Spinal mobility represented by the BASMI lateral spinal flexion assessment

6. C-reactive protein (acute phase reactant)

ASAS response criteria (ASAS 20)

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

The ASAS Response Criteria (ASAS 20) was defined as an improvement of ≥ 20% and ≥ 10 unit on a scale of 100 in at least 3 of the 4 main domains and no worsening of ≥ 20% and ≥ 10 unit on a scale of 100 in the remaining domain.

ASAS response criteria (ASAS 40)

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

ASAS 5/6 improvement criteria

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

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.

5.5.2 Ankylosing spondylitis disease activity score (ASDAS)

The ASDAS (Sieper et al 2009, Lukas et al 2009) is a composite index to assess disease activity in AS.The ASDAS-C-reactive protein (CRP) will be utilized to assess the disease activity status.

Parameters used for the ASDAS include:

- Total back pain (BASDAI question 2)
- Patient global assessment of disease activity
- Peripheral pain/swelling (BASDAI question 3)
- Duration of morning stiffness (BASDAI question 6)
- CRP in mg/liter

Disease activity states: inactive disease, low disease activity, high disease activity, and very high disease activity. The 3 values selected to separate these states were < 1.3 between inactive disease and low disease activity, < 2.1 between moderate disease activity and high disease activity, and > 3.5 between high disease activity and very high disease activity. Selected cutoffs for improvement scores were a change ≥ 1.1 unit for “minimal clinically important improvement” and a change ≥ 2.0 units for “major improvement” (Machado et al 2011).

The following formula will be used to derive ASDAS-CRP:

ASDAS-CRP = 0.121 x total back pain + 0.110 x patient global + 0.073 x peripheral pain/swelling + 0.058 x duration of morning stiffness + 0.579 x Ln(CRP+1).

ASDAS-ESR = 0.08 x Back Pain + 0.07 x Duration of Morning Stiffness + 0.11 x Patient Global + 0.09 x Peripheral Pain/Swelling + 0.29 x √(ESR)

All assessments will be performed in 0-10 scale.

5.5.3 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 axSpA:

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 2 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.

At least 4 questions should be non-missing to calculate the BASDAI score. Otherwise, BASDAI score will be missing (Haywood 2002). If both Q5 and Q6 are missing or one of Q1 to Q4 is missing the total sum should be divided by 4 instead of 5. If two of Q1 to Q4 is missing the sum should be divided by 3. BASDAI 50 response is defined as at least a 50% improvement (decrease) in total BASDAI score, as compared to the Baseline total BASDAI score.

5.5.4 Bath ankylosing spondylitis functional index (BASFI)

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those subjects with AS. The ten questions were chosen with a major input from subjects with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the subjects' ability to cope with everyday life. A 100 mm VAS is used to answer the questions. The mean of the ten questions gives the BASFI score – a value between 0 and 10. If there are missing questions the average of the non-missing items is used (Braun 2009, van Tubergen 2001).

5.5.5 ASAS Health Index

The ASAS health index is a linear composite measure and contains 17 items (dichotomous response option: "I agree" and "I do not agree").

Each statement on the ASAS Health Index is given a score of 1 = I agree OR 0 = I do not agree. All item scores are summed up to give a total score that ranges from 0 (good functioning) to 17 (poor functioning). Items No 7 and 8 are not applicable for all patients. For those patients who ticked the response "not applicable", the sum score is analysed based on n=16 or n=15, respectively.

A total score can be analysed if no more than 20% of the data are missing. The total score is calculated as follows for respondents with one to a maximum of three missing responses:

$$\text{sumscore} = \frac{x}{17 - m} \times 17$$

x = Item summation score

m = Number of missing items

Cases with more than three missing responses cannot be allocated a total score.

5.5.6 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 lumbar flexion (cm)
2. tragus-to-wall distance (cm)
3. lumbar flexion (modified Schober) (cm)
4. intermalleolar distance (cm)
5. cervical rotation angle (cm)

Additionally, the following assessments should be taken:

6. chest expansion
7. occiput-to-wall distance

The assessments *A* of the first five components into the scores *S* using the equations are given in Table 5-1(van der Heijde et al, 2013).

Table 5-1 Equations for the conversion of the assessments A into scores S for the five components of the BASMI linear

	S = 0 if	Between 0 and 10	S = 10 if
Lateral lumbar flexion* (cm)	A ≥ 21.1	S = (21.1 – A)/2.1	A ≤ 0.1
Tragus-to-wall distance* (cm)	A ≤ 8	S = (A – 8)/3	A ≥ 38
Lumbar flexion (modified Schober) (cm)	A ≥ 7.4	S = (7.4 – A)/0.7	A ≤ 0.4

	S = 0 if	Between 0 and 10	S = 10 if
Intermalleolar distance (cm)	A ≥ 124.5	S = (124.5 – A)/10	A ≤ 24.5
Cervical rotation angle*(°)	A ≥ 89.3	S = (89.3 – A)/8.5	A ≤ 4.3

* For lateral lumbar flexion, tragus-to-wall distance, and cervical rotation the average of right and left should be taken.
If a score lies beyond the range 0-10, the values 0 or 10 have to be used, respectively.
For facilitating computer calculations with "if… then … else" fields in a table calculation program such as Microsoft Excel, the limits of the linear ranges are also given. The $BASMI_{linear}$ is the mean of the five scores.

5.5.7 ASAS-NSAID Score

The recommendations by ASAS (Dougados 2010) will be used to score each patient's NSAID use during specific time periods. The components that go into the calculation of the score is the type of NSAID, average daily dose, length in days of the time period of interest and the number of days with NSAID intake within the time period of interest. The final score should be between 0 and 100 but can in rare cases be larger than 100.

The scoring of NSAIDs is described below.

Score	Intake
0	No intake
100	150 mg diclofenac, 600 mg etodolac, 150 mg indometacin, 20 mg piroxicam, 1000 mg naproxen, 90 mg etoricoxib, 200 mg ketoprofen, 20 mg tenoxicam,200 mg aceclofenac, 200 mg flurbiprofen, 15 mg meloxicam, 400 mg celecoxib, 2400 mg ibuprofen, 400 mg phenylbutazone.

The CRF provided dose information will be handled as follows:

- Doses > maximum dose will be scored as > 100
- Missing doses will be scored with maximum daily dose for the current NSAID (i.e. score of 100)

Drug start and end dates are needed in order to know the number of days an NSAID was prescribed. In case they are missing, the following rules will be used:

- Missing start dates will assume the start date of medication is Day -28 (i.e. prior to start of study drug)
- Missing end dates will assume the end date of medication is the patient's last day in the Study

- If the study drug is ongoing when the patient discontinues then the drug end date will be equal to the day of discontinuation. The period end date will also end on the day of discontinuation

The table below presents the score associated with the dosing frequency as specified by the ASAS definition and how the different database entries will be categorized. The frequency was not consistently specified in the ASAS publication, the below categorization was selected.

Table 5-2 Mapping of dosing frequency to NSAID score

Frequency	Scores	Database entry
Patient did not take any NSAID during the period of interest	0/7	
<1 day/week	0.5/7	Q2W, MISSING, PRN, UNK, ASNEEDED, QM, Q4W, Q3W
≥1 − <3 days/week	2/7	Q1W, WEEKLY, BIW
≥3 − <5 days/week	4/7	TIW, QIW
≥5 − <7 days/week	6/7	
Everyday	7/7	TID, BID, DAILY, Q24H, QID, QD
Note: Q2W=every 2 weeks, PRN=as needed, UNK=unknown, Q1W=one a week, BIW=twice a week, TIW=three times a week, TID=three times a day, BID=twice a day, QIW= four times a week, Q24H=QID=QD=one a day, QM=one a month; Q4W=one every 4 weeks; Q3W=one every 3 weeks.		

To calculate the NSAID cumulative score the following formula will be used for each NSAID being taken:

100*(Daily dose / pre-specified max dose) * frequency score * (min(medication end date, period end date) – max(medication start date, period start date) + 1 = range of days patient used the medication) / number of days the patient was in the period.

In case a patient takes more than one type of NSAID, changes the dose or the frequency of NSAID during the period of interest, additional scores will be calculated for each new combination and the final score for that patient is the sum of all scores.

5.6 Rule of exclusion criteria of analysis sets

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
INCL01	Patients have not signed Informed Consent Form prior to initiation of any studyrelated procedure	INCLUDE IN EVERYTHING	0
INCL02a	Age criteria not met	INCLUDE IN EVERYTHING	0
INCL02b	Pregnant or Lactating female patients	INCLUDE IN EVERYTHING	0
INCL03	Are modified New York Criteria for Ankylosing Spondylitis fulfilled or met Is No in Modified New York criteria form	INCLUDE IN EVERYTHING	0
INCL04	BASDAI Average Score less than 4 at baseline	INCLUDE IN EVERYTHING	0
INCL05	BASDAI Question 2 is less than 4 cm at baseline	INCLUDE IN EVERYTHING	0
INCL06	Total back pain is less than 40 mm at baseline	INCLUDE IN EVERYTHING	0
INCL07	Patient is not on at least 2 different NSAIDs at the highest recommended dose for at least 4 weeks in total in the past, prior to randomization	INCLUDE IN EVERYTHING	0
INCL08a	Patient has not reported regular intake of NSAIDs of at least 50 percent of the highest recommended dose at Screening	INCLUDE IN EVERYTHING	0
INCL08b	Patient with prior TNFα alpha inhibitor therapy has not reported regular intake of NSAIDs of at least 50 percent of the highest recommended dose at baseline after the appropriate washout.	INCLUDE IN EVERYTHING	0
INCL09	Patient is not on a stable dose of NSAIDs for at least 2 weeks before randomization.	INCLUDE IN EVERYTHING	0
INCL10	Patient has previously been on a TNF alpha inhibitor however, an appropriate washout period was not maintained prior to randomization	INCLUDE IN EVERYTHING	0
INCL11	Pt on TNF alpha l and not exprncd inadequate response to previous or current trtmnt at approved dose for at least 3M prior to Rndz or not intolerant to at least 1 administration of anti TNF alpha	INCLUDE IN EVERYTHING	0
INCL11a	patients that did not tolerate TNF alpha inhibitor or that were inadequate responder are eligible for study however the reason for discontinuation is equal other in Concomitant medication CRF	INCLUDE IN EVERYTHING	0
INCL12	If a patient taking MTX or sulfasalazine continues taking, but either took MTX prevoiusly for shorter than 3 Months or the	INCLUDE IN EVERYTHING	0

	dose was not stable in the last 4 week prior to randomization		
INCL13	Patient on MTX is not on stable folic acid supplementation before randomization	INCLUDE IN EVERYTHING	0
INCL14	Patient has not discontinued DMARD 4 weeks prior to randomization	INCLUDE IN EVERYTHING	0
INCL15	Patients taking systemic corticosteroids have to be on a stable dose	INCLUDE IN EVERYTHING	0
EXCL01	Chest Xray or MRI with evidence of ongoing infectious or malignant process, obtained within 3 months of screening and evaluated by a qualified physician	INCLUDE IN EVERYTHING	0
EXCL02	Patients taking high potency opioid analgesics eg methadone hydromorphone and morphine	INCLUDE IN EVERYTHING	0
EXCL03	Previous exposure to Secukinumab or any other biologic drug directly targeting IL17 or IL17 receptor	INCLUDE IN EVERYTHING	0
EXCL04	Use of any IND and or devices within 4W of RNDMZ or period of 5 halflives of investigational drug or participation in another study in the same indication during enrollment in this study	INCLUDE IN EVERYTHING	0
EXCL05	History of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes	INCLUDE IN EVERYTHING	0
EXCL06	Any therapy by intraarticular injections example corticosteroid within 4 weeks before randomization	INCLUDE IN EVERYTHING	0
EXCL07	Any intramuscular corticosteroid injection within 2 weeks before randomization	INCLUDE IN EVERYTHING	0
EXCL08	Patients previously treated with any biological immunomodulating agents except those targeting TNF alpha	INCLUDE IN EVERYTHING	0
EXCL09	Patients who have taken more than two anti TNF alpha agents	INCLUDE IN EVERYTHING	0
EXCL10	Previous treatment with any cell depleting therapies including but not limited to anti CD20 or investigational agents example CAMPATH anti-D4 antiCD5 antiCD3 antiCD19	INCLUDE IN EVERYTHING	0
EXCL11	Pregnant or nursing lactating women where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test	INCLUDE IN EVERYTHING	0
EXCL12	Women of childbearing potential not using effective contraception methods during entire study or longer if required by locally approved prescribing info	INCLUDE IN EVERYTHING	0
EXCL13	Active ongoing inflammatory diseases other than AS that might confound the evaluation of	INCLUDE IN EVERYTHING	0

	the benefit of Secukinumab therapy, including inflammatory bowel disease or uveitis		
EXCL14	Underlying 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	INCLUDE IN EVERYTHING	0
EXCL15	Significant medical problems or diseases or very poor functional status unable to perform self care	INCLUDE IN EVERYTHING	0
EXCL16	History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as SGOT AST and SGPT ALT alkaline phosphatase or serum bilirubin	INCLUDE IN EVERYTHING	0
EXCL17	History of renal trauma glomerulonephritis or patients with one kidney only or a serum creatinine level exceeding 1.5 milligram per decilitre 132.6 micromol per litre	INCLUDE IN EVERYTHING	0
EXCL18	Screening total WBC count less than 3000 per micro litre or platelets less than 100000 per microlitre or neutrophils less than 1500 per micro litre or hemoglobin less than 85 gram per litre	INCLUDE IN EVERYTHING	0
EXCL19	Active systemic infections during the last two weeks prior to randomization exception: common cold	INCLUDE IN EVERYTHING	0
EXCL20a	History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection.	INCLUDE IN EVERYTHING	0
EXCL20b	History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection	INCLUDE IN EVERYTHING	0
EXCL21	Known infection with human immunodeficiency virus HIV hepatitis B or hepatitis C at screening or randomization	INCLUDE IN EVERYTHING	0
EXCL22	History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years	INCLUDE IN EVERYTHING	0
EXCL23	Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial	INCLUDE IN EVERYTHING	0
EXCL24	Inability or unwillingness to undergo repeated venipuncture Example because of poor tolerability or lack of access to veins	INCLUDE IN EVERYTHING	0
EXCL25	Inability or unwillingness to receive injections with PFS	INCLUDE IN EVERYTHING	0
EXCL26	Any medical or psychiatric condition which in the Investigators opinion, would preclude the	INCLUDE IN EVERYTHING	0

	participant from adhering to the protocol or completing the study per protocol		
EXCL27	Donation or loss of 400 mL or more of blood within 8 weeks before dosing	INCLUDE IN EVERYTHING	0
EXCL28	History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization	INCLUDE IN EVERYTHING	0
EXCL29	Plans for administration of live vaccines during the study period or 6 weeks prior to randomization	INCLUDE IN EVERYTHING	0
EXCL30	Patients who are intolerant to NSAIDs	INCLUDE IN EVERYTHING	0
COMD01	Concomitant use of Etanercept during the study	INCLUDE IN EVERYTHING	0
COMD02	Concomitant use of Infliximab during the study	INCLUDE IN EVERYTHING	0
COMD03	Concomitant use of following medications during the study Adalimumab golimumab certolizumab	INCLUDE IN EVERYTHING	0
COMD04	Concomitant use of Leflunomide during the study	INCLUDE IN EVERYTHING	0
COMD05	Systemic corticosteroids use within 2 weeks prior to Baseline	INCLUDE IN EVERYTHING	0
COMD06	Intra articular steroids injections use during the study	INCLUDE IN EVERYTHING	0
COMD07	MTX dose is changed between BL and W12 for reason other than an AE	INCLUDE IN EVERYTHING	0
COMD08	Patient taking MTX do not take folic acid supplementation during the study	INCLUDE IN EVERYTHING	0
COMD09	The corticosteroid dose reduced by more than 1 mg prednisone equivalent every 4 weeks	INCLUDE IN EVERYTHING	0
COMD10	Pts regularly using NSAIDs low strength opioids paracetamol acetaminophen not on stable dose for at least 2W before randomization to allow inclusion Or not on a stable dose in the study up to W4	INCLUDE IN EVERYTHING	0
COMD11	Live vaccines less than 6 weeks before randomization or Live vaccines given before 12 weeks after last study treatment administration.	INCLUDE IN EVERYTHING	0
COMD12	Incorrect study medication given OR additional study medication given	INCLUDE IN EVERYTHING	0
COMD13	Patient not discontinued study drug despite severe or serious AE that is not compatible with administration of study medication	INCLUDE IN EVERYTHING	0

COMD14	Concomitant use of Systemic corticosteriods greater than 10mg prednisone equivalent	INCLUDE IN EVERYTHING	0
COMD15	No Unstable dose of MTX other DMARD Any investigational treatment or participation in any interventional trial & Analgesics other than paracetamol/acetaminophen or low strength opinions PRN	INCLUDE IN EVERYTHING	0
TRT01	Incorrect, missed or partial doses of study medication administered	INCLUDE IN EVERYTHING	0
OTHR01	Urinalysis not performed.	INCLUDE IN EVERYTHING	0
OTHR02	Physical examination not performed.	INCLUDE IN EVERYTHING	0
TRT02	Intake of low strength opioids is reported 24 hours before a visit with disease activity.	INCLUDE IN EVERYTHING	0
TRT03	Mishandling of investigational product.	INCLUDE IN EVERYTHING	0
TRT04	During intermediate storage of IMP no Tmin/Tmax data available. According to decision of Novartis QP medication should not be used, but was already dispensed to patient.	INCLUDE IN EVERYTHING	0
TRT05	Time frame between 2 IMP injections not respected.	INCLUDE IN EVERYTHING	0
OTHR03	Patient is outside the recommended visit window, not followed as per protocol.	INCLUDE IN EVERYTHING	0
OTHR04	ECG was not performed as per assessment schedule.	INCLUDE IN EVERYTHING	0

Analysis set exclusions based on population codes

Analysis set	Population codes that cause a subject to be excluded
RAN	NA
SAF	2, 3, 6
FAS	1, 3

Population code text

Population Code	Population code text
0	INCLUDE IN EVERYTHING
1	EXCLUDE FROM FULL ANALYSIS SET (FAS)
2	EXCLUDE FROM SAFETY SET (SAF)
3	EXCLUDE FROM FAS AND SAF

6 Reference

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.