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US Clinical Development and Medical Affairs

AIN457/Secukinumab

CAIN457FUS06 / NCT03350815

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

Statistical Analysis Plan (SAP)

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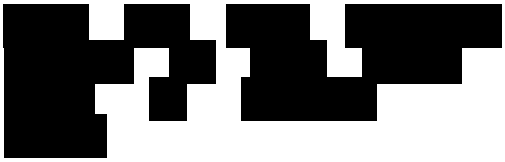
Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
14-Aug-2018	Prior to DB lock	As advised in the RAP meeting	Nonresponder Set definition added.	Section 2.2
			Subgroup efficacy analyses based on two subgroups defined by the TNF-alpha inhibitor status are added.	Section 2.2.1
			Information on additional analyses are added.	Section 2.5.2 and 2.7.2
			Additional analysis of change from Week 16 in total BASDAI using mixed-effects model repeated measures (MMRM) is added.	Section 2.7.2
			Multiple imputation is removed for secondary [redacted] efficacy variables.	Section 2.7.3
			[redacted]	
			Information on calculation of 95% confidence interval is added.	Section 5.4.4 and 5.4.5
			SAS code for MMRM analysis added	Section 5.4.3

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
01-Apr-2021	Prior to DB Lock		Visit window for baseline and Week 52 assessments	Section 2.1.2
			Removed reference to PASI75 and mNAPSI	Section 2.1.3
			Defined Enrolled Set for safety analyses and removed Randomized Set	Section 2.2
			Medical history details added	Section 2.3.3
			Duration of exposure defined and compliance added	Section 2.4.1
			Elaborated non-responder imputation and removed the wording "post-randomization" for non-responder imputation	Section 2.5.3
			Removed ANCOVA model for analysis of some secondary efficacy variables	Section 2.7.2
			Removed the wording "post-randomization" for non-responder imputation and removed LOCF for handling missing data	Section 2.7.3
			Defined Treatment-Emergent Adverse Events separately for Treatment Periods 1 and 2 and entire treatment period	Section 2.8.1
			Described legal requirements of ClinicalTrials.gov	
			Described analyses for laboratory data	Section 2.8.3
			Updated analysis for ECG data	Section 2.8.4.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Updated analysis for vital signs	Section 2.8.4.2
			Replaced VAS with NRS and updated with more details	Section 2.11
				
			Statements about not using multiple imputation for continuous secondary efficacy variables, using MMRM, not using LOCF for handling missing data and definition of Enrolled Set for safety analyses, are added	Section 4
			Medical history date of diagnosis imputation rules added	Section 5.1.4
			Formatting update	Section 5.2
			Added more details on multiple imputation	Section 5.4.1
			Described rules for protocol deviations with their severity codes for excluding patients from analysis sets	Section 5.5
08-Jul-2021	Post DB Lock		Added details on duration of exposure for entire treatment period	Section 2.4.1
			Added details on figures for entire treatment period	Section 2.5.2
			Added details on analyses considering baseline for Treatment Period 2 and figures for entire treatment period	Section 2.7.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Added details on analyses considering baseline for Treatment Period 2 and figures for entire treatment period	Section 2.13

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List of abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT/SGPT	Alanine aminotransferase/serum glutamic pyruvic transaminase
AS	Ankylosing Spondylitis
ASAS	Ankylosing SpondyloArthritis International Society
ASAS-HI	ASAS Health Index
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST/SGOT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase
ATC	Anatomical Therapeutic Chemical
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
[redacted]	[redacted]
BMI	Body mass index
BSL	Baseline
CI	Confidence interval
COX	Cyclooxygenase
CRF	Case Report/Record Form (paper or electronic)
CRP	C-reactive protein
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DMARD	Disease Modifying Anti-rheumatic Drug
eCRF	Electronic Case Report/Record Form
ECG	Electrocardiogram
FACIT-Fatigue©	Functional Assessment of Chronic Illness Therapy – Fatigue
FCS	Fully conditional specification
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
hCG	Human chorionic gonadotropin
HGB	Hemoglobin
HIV	Human immunodeficiency virus
HLA-B27	Human leukocyte antigen B27
[redacted]	[redacted]
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Inadequate responder
IRT	Interactive Response Technology
MAR	Missing at random
[redacted]	[redacted]
MedDRA	Medical dictionary for regulatory activities

mg	milligram
MMRM	Mixed-effects model repeated measures
MRI	Magnetic resonance imaging/image
MTX	Methotrexate
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
PFS	Prefilled syringe
PPD	Purified protein derivative
PRO	Patient Reported Outcome
PsA	Psoriatic arthritis
PT	Preferred term
RBC	Red blood cell
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
s.c.	Subcutaneous(ly)
SE	Sleep efficiency
SOC	System Organ Class
SpA	Spondyloarthritis
[redacted]	[redacted]
SV	Subject visit
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TFL	Tables, Figures, Listings
TNF	Tumour Necrosis Factor
[redacted]	[redacted]
WBC	White blood cell

1 Introduction

This document describes the planned statistical methods for all safety and efficacy analyses which will be performed in the Phase 4 clinical trial AIN457FUS06.

This document describes the planned statistical analysis methodologies which will be performed to estimate the difference in clinical response between 300 mg and 150 mg of secukinumab at Week 52, which follows randomization to dose escalation at Week 16 for patients with ankylosing spondylitis who inadequately respond to open-label secukinumab 150 mg in the Phase 4 Clinical Trial AIN457FUS06.

Analysis plans in this document refer to the related statistical analysis sections in Clinical Study Report (CSR).

Data will be analyzed by NBS CONEXTs (formerly known as Novartis Product Lifecycle Services) using Statistical Analysis Software (SAS®, version 9.4), according to Section 9 (Data Analysis) of the study protocol which is available in Appendix 16.1.1 of the CSR.

Additional detailed information regarding the analysis methodology will be contained in the Appendix Section 16.1.9 of CSR.

Please refer to the following document:

Clinical Protocol CAIN457FUS06

1.1 Study design

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

There are 3 study periods:

1. **Screening:** A screening period will take place over two separate visits, with the first visit used to assess eligibility and to washout prohibited medications (up to 11 weeks). The second screening visit, which will occur at a minimum of 2 weeks prior to the baseline visit for all patients. [redacted] **Note: Patients that do not require a washout, and who satisfy all inclusion and none of the exclusion criteria at the first screening visit can initiate the second screening visit one week after their first screening visit.**

2. **Treatment Period 1:** Patients who meet all of the inclusion criteria and none of the exclusion criteria will have a Baseline Visit performed to start Treatment Period 1. During this 16-week period, all patients will receive open-label secukinumab 150 mg [1 x 1.0mL s.c.] at baseline, Weeks 1, 2, 3, 4, 8, and 12.

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

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

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

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

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

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

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

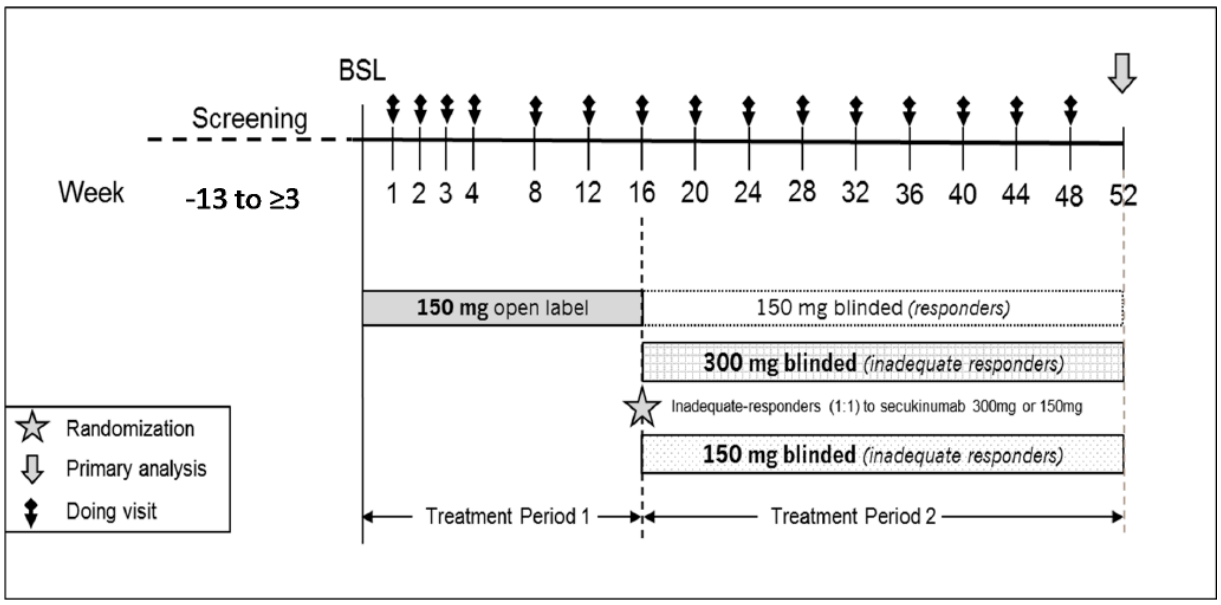
b. **Inadequate responders** will enter Treatment Period 2 and will be randomized (1:1, double-blinded) to secukinumab 300 mg or secukinumab 150 mg very 4 weeks through Week 48. Subjects will know that they are on secukinumab, but will be blinded to dose, as they will not know whether they are receiving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

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

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

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

Figure 1 Study design

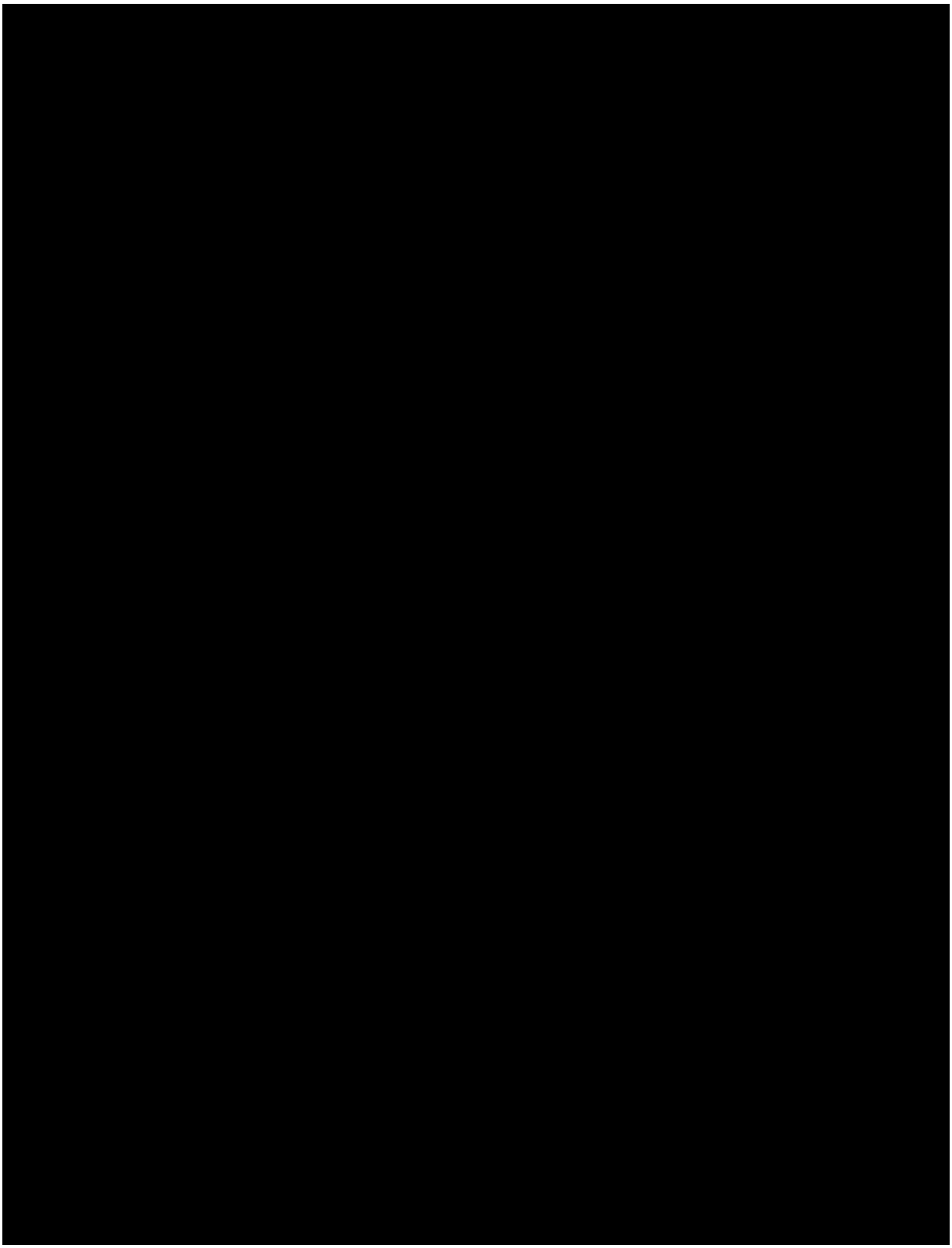


1.2 Study objectives and endpoints

Objective	Endpoint
Primary objective	
To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving ASDAS inactive disease (< 1.3) status who did not meet ASDAS inactive disease criteria at Week 12 and Week 16.	ASDAS inactive disease response (yes, no) at Week 52.
Secondary objectives	
To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving a ASDAS clinically important improvement from their Week 16 ASDAS score (reduction in ASDAS ≥1.1 from Week 16)	Reduction in ASDAS ≥1.1 from Week 16 (yes, no)
To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the change from Week 16 in the total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)	Change from Week 16 in total BASDAI
To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving BASDAI50 response	BASDAI50 response (yes, no)
To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving an Assessment of	ASAS20 response (yes, no)

Spondyloarthritis International Society criteria 20 response (ASAS20)	
To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving ASAS40 response	ASAS40 response (yes, no)
To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on the proportion of subjects achieving ASAS partial remission (a value not above 2 units in each of the four main domains on a scale of 10)	ASAS partial remission (yes, no)
To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on change from Week 16 in the total score of ASAS Health Index (ASAS-HI)	Change from Week 16 in ASAS-Health Index
To estimate the difference between secukinumab 300 mg and secukinumab 150 mg blinded treatment groups at Week 52 based on change from Week 16 in the total score of FACIT-Fatigue	Change from Week 16 in FACIT-Fatigue
The overall safety and tolerability of secukinumab	

[redacted]



2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by NBS CONEXTs (formerly known as Novartis Product Life-Cycle Services).

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

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).

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

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

2.1.1 General definitions

Study Treatment

The following are the investigational treatments:

- Secukinumab 150 mg provided in 1.0 mL in PFS for s.c. injection.
- Secukinumab 300mg provided in 1.0 mL PFS for s.c. injection.

Study treatment start and end date

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

Study treatment 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 of the core study.

Study day

Study day will be calculated as (event date – study drug start date + 1 day) for events that occurred on or after study drug start date (e.g. visit, lab samples, AEs). For events prior to study drug start date (e.g., time of diagnosis), study day will be negative and calculated as (event date – study drug start date). Note that study drug start date is study day 1 and the day before study drug start date is study day -1 (i.e. no study day 0).

Due to the study drug dosing schedule, one month will be considered as 28 days. However, for ”time since event” data (e.g., medical history), one month will be considered as 365.25/12 days for events that occurred prior to study Day 1.

Baseline and post-baseline definitions

In general, a baseline value refers to the last measurement available prior to administration of the first dose of study treatment. A post-baseline value refers to a measurement taken after the first dose of study treatment.

For Treatment Period 2, Week 16 assessments will be considered the baseline for all analyses performed during this period.

Treatment Period

There are 2 treatment periods for this study defined as:

Treatment Period 1 is defined as the 16-week open-label treatment period starting from baseline until Week 16.

Treatment Period 2 is a 36-week, double-blind treatment period starting from Week 16 until Week 52.

Lost to follow up

Patients whose study completion status is unclear because they fail to appear for study visits without stating an intention to withdraw.

On-treatment period

The period where the patients are exposed to the study treatment. For this study the treatment phase consists of 52 weeks.

2.1.2 Visits windows

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 the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. The visit windows are shown in [redacted] These apply to measurements taken at every visit.

For assessments collected less often different visit windows will be applied as detailed below.

> 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 in [redacted]

Of note, subjects are allowed to have gaps in visits.

[redacted]

For data which are **not** collected at every visit (e.g., ASAS-HI, [redacted], visit windows defined in [redacted] will be combined. For example, if an assessment is at Week 12 and Week 24 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 183 (combining Week 16 to Week 24). If more than one assessment falls into the interval, the rules defined in Section 2.1.3 below are applied.

2.1.3 Multiple assessments within visit windows

When there are *multiple assessments* in a particular visit window, the following rules are applied to select one value "representing" the subject in summary statistics in a visit window (See [redacted]

For baseline assessment definition see Section 2.1.1. For post-baseline visit windows the following applies (unless otherwise specified):

- for *quantitative variables*, the *closest* to the actual visit is chosen (if two assessments have the same distance, then the earlier one will be chosen);
- for *qualitative variables*, the *worst* record is selected. It is noted that in the analyses performed, *worst* case is always well defined.
- in cases where qualitative variables are derived from quantitative variables (e.g., ASDAS, BASDAI50, ASAS20, ASAS40, ASAS partial remission, and reduction in ASDAS>=1.1 from Week 16), the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

[redacted]

2.2 Analysis sets

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

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

Note: For safety analyses, the Enrolled Set will consist of enrolled patients for the initial 16-week, Treatment Period 1 who received at least one dose of the open-label treatment, secukinumab 150 mg.

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

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

Full Analysis Set: The Full Analysis Set comprises all patients to whom study treatment has been assigned by randomization. According to the intent-to-treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

Non-responder Set: The Non responder Set consists of all patients who are labeled as non-responders at the end of Treatment Period 1 and do not enter Treatment Period 2.

2.2.1 Subgroup of interest

Subgroup analyses will be performed for all the efficacy variables based on the TNF-alpha inhibitor status (naive, inadequate responder).

2.3 Patient disposition, demographics and other baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristics and the number and percentage of patients in each category will be presented for categorical variables for each treatment group. The summaries will be reported for Enrolled Set, Responder Set, Safety Set, Full Analysis Set (FAS), and Nonresponder Set.

2.3.1 Patient disposition

The number and percentage of patients screened, completed Treatment period 1 and 2, discontinued Treatment Period 1 or 2 including a summary of reasons for discontinuations will be presented for Enrolled Set and Full Analysis Set. In addition, the reasons for screen failures will be provided.

All patient disposition data will be listed.

Number and percentage of patients with pandemic related protocol deviations will be tabulated for each treatment period. The pandemic period is considered to be a period starting from 1st March 2020 onwards.

2.3.2 Patient demographic and other baseline characteristics

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

The following demographic and baseline variables, if collected, will be summarized:

Continuous variables:

- Age (which is derived from date of birth and the screening assessment date)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

Categorical variables:

- Sex
- Race
- Ethnicity
- Child-bearing status (for females only)Age (<65 and >=65)

Smoking status at Baseline will be summarized.

In addition to this, data for tuberculosis risk assessment, ECG evaluation and chest X-ray or MRI, as collected from respective CRF pages at Screening Visit 2, will be summarized.

2.3.3 Medical History

Any condition entered on the *Medical History* CRF will be coded using the MedDRA dictionary. These will be summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary for the Enrolled Set, the Responder Set, the Nonresponder Set and by treatment group for the Safety Set. Summaries for cardiovascular medical history as collected on *Cardiovascular Medical History* CRF will be provided as well.

Ankylosing Spondylitis disease background including time (years) since axial symptom onset, time (years) since diagnosis of ankylosing spondylitis, TNF-alpha exposure, inhibitor treatment and response status along with history of extra-axial involvement, will be summarized at Screening Visit 1 for the Enrolled Set, the Responder Set, and by treatment group for the Full Analysis Set and Safety Set.

Smoking history and *alcohol history* as collected at baseline, will be summarized for the Enrolled Set, the Responder Set, and by treatment group for the Full Analysis Set and Safety Set.

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

2.4.1 Study treatment / compliance

Study Treatment

The summaries by treatment group will be performed by the actual treatment received (as follows) for every visit until Week 16.

Treatment groups in Treatment Period 1:

- Secukinumab 150 mg

In Treatment Period 2, the summaries by treatment group will be performed by the actual treatment received (as follows) for every visit up to Week 52, including patients who switched at Weeks 16.

Treatment groups in Treatment Period 2:

- Secukinumab 150 mg - 300 mg (IR)
- Secukinumab 150 mg - 150 mg (IR)
- Secukinumab 150 mg – 150 mg (R)

where, R: Responders and IR: Inadequate Responders

Treatment groups in entire treatment period:

- Secukinumab 150 mg

- Secukinumab 300 mg

Duration of exposure

The duration of exposure (in days) will be summarized by means of descriptive statistics for the Enrolled Set, the Responder Set, and each treatment group for the Safety Set. In addition, the number of subjects with exposure of at least certain time thresholds will be displayed (e.g. any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, ≥ 8 weeks, etc.).

For Treatment Period 1, the end date for the calculation of duration of exposure will be the earlier of:

- Date of last injection in Treatment Period 1 + 84 days, and
- Date of first injection in Treatment Period 2

For Treatment Period 2, the end date for the calculation of duration of exposure will be the date of last injection in Treatment Period 2 + 84 days.

For entire treatment period, the end date for the calculation of duration of exposure will be the date of last injection + 84 days.

For patients with death as an event, end date for calculation of duration of exposure will be the date of death if it is earlier than the date of last injection + 84 days.

Duration of exposure (years) = duration of exposure (days) / 365.25

Duration of exposure (100 patient years) = duration of exposure (years) / 100

Compliance

Compliance will be calculated based on documented study drug administrations and syringe counts and displayed by treatment group. It is calculated as follows:

Compliance (%) = 100*(total no. of injections administered) / (no. of injections prescribed). Compliance is expected to be 100%, unless temporary interruption is needed for safety reasons.

The analyses of duration of exposure and compliance described above will be done for Treatment Period 1 and Treatment Period 2.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant therapies

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 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. Summaries will be presented for the Enrolled Set, the Responder Set, and each treatment group for the Safety Set.

Medications will be presented in alphabetical order, by Anatomical Therapeutic Chemical (ATC) classification codes and grouped by anatomical main group. Tables will show the overall number and percentage of patients 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 surgeries and procedures will be summarized by primary system organ class and MedDRA preferred term.

In addition, prior and concomitant medication data will be listed.

Rescue medication
Rescue medication is not permitted during the study.

2.5 Analysis of the primary objective

The primary objective is to estimate the difference between secukinumab 300 mg and secukinumab 150 mg treatment groups at Week 52 based on the proportion of subjects achieving ASDAS inactive disease (<1.3) status who did not meet ASDAS inactive disease criteria at Week 12 and Week 16.

2.5.1 Primary endpoint

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

The primary analysis will be done on Full Analysis Set (FAS).

2.5.2 Statistical hypothesis, model, and method of analysis

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

The primary efficacy variable will be analyzed at each time point until Week 52 using a logistic regression model with treatment, TNF-alpha inhibitor status (naive, inadequate responder), and Week 16 body weight as explanatory variables (Stokes, Davis, and Koch, 2012). The odds ratios and 95% confidence intervals for the odds ratios will be reported, based on the fitted model.

Number and percentages for ASDAS inactive disease response will also be reported for each treatment group, by TNF-alpha inhibitor status (naive, inadequate responder) by visit. A line plot for ASDAS inactive disease responders (%) from Week 16 to Week 52 will be presented. A similar line plot will be presented by TNF-alpha inhibitor status.

A line plot for ASDAS inactive disease responders (%) over entire treatment period (from Week 1 to Week 52) will be presented. A similar line plot will be presented by TNF-alpha inhibitor status.

Also, number and percentages for the patients with ASDAS inactive disease response in Treatment Period 1 who entered Treatment Period 2 will be provided based on the below criteria:

- Patients receiving 150mg (open label) (Enrolled Set)
- Patients receiving randomized 300mg and 150mg (Randomized Set)
- Patients who are responders (Responder Set)
- Patients who are nonresponders (Nonresponder Set)

In addition, the above analysis will be done by TNF-alpha inhibitor status and by visit.

2.5.3 Handling of missing values/censoring/discontinuations

Patients who discontinue prematurely for any reason will be considered nonresponders from the time they discontinued through Week 52. Also, patients who do not have the required data to compute response (ASDAS components) at the specific time point will be classified as nonresponders.

In an additional analysis, missing data for ASDAS inactive disease response will be imputed using multiple imputation. Details for multiple imputation is presented in Appendix Section 5.4.

2.5.4 Supportive analyses

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

The analysis will be performed at each time point in Treatment Period 2.

2.6 Analysis of the key secondary objective

Not applicable.

2.6.1 Key secondary endpoint

Not applicable.

2.6.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.6.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

Refer to Section 1.2 for the list of secondary objectives.

2.7.1 Secondary endpoints

The secondary efficacy variables are the following (see Section 2.11 for details of the assessments from which the efficacy variables are derived):

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

8. Change from Week 16 in FACIT-Fatigue

2.7.2 Statistical hypothesis, model, and method of analysis

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

Reduction in ASDAS ≥1.1 from Week 16

Reduction in ASDAS ≥1.1 from Week 16 (yes, no) will be analyzed at each time point in Treatment Period 2 until Week 52 using a logistic regression model with treatment, TNF-alpha inhibitor status (naive, inadequate responder), and Week 16 body weight as explanatory variables. The odds ratios and 95% confidence intervals for the odds ratios will be reported, based on the fitted model. Similar analysis will be performed for the subgroups defined by TNF-alpha inhibitor status.

A 95% confidence interval for the difference, at each time point in Treatment Period 2 until Week 52, between the two treatment groups in the proportion of patients who have reduction in ASDAS≥1.1 from Week 16 will be calculated using the normal approximation to the binomial distribution for the Full Analysis Set.

Number and percentages of patients with reduction in ASDAS≥1.1 from Week 16 will also be reported for each treatment group in each treatment period by visit and similarly by TNF-alpha inhibitor status (naive, inadequate responder).

Change from Week 16 in total BASDAI

Analysis of change from Week 16 in total BASDAI score will be performed using mixed-effects model repeated measures (MMRM) with treatment, visit, and TNF-alpha inhibitor status (naive, inadequate responder) as factors, Week 16 score and Week 16 weight as covariates, and treatment-by-visit and Week 16-by-visit as interaction terms (Diggle, Heagerty, and Liang KY, 2002). The least-squares (LS) mean difference between secukinumab 150 mg - 300mg (IR) and secukinumab 150 mg - 150mg (IR) will be presented along with the corresponding 95% CI.

Similar analysis will be performed for the subgroups defined by TNF-alpha inhibitor status.

Descriptive summary statistics for change from baseline in Treatment Period 1 and change from Week 16 in Treatment Period 2, for total BASDAI score for each visit will be provided. Similarly, descriptive summary statistics will also be provided by TNF-alpha inhibitor status.

Analysis of change from Week 16 in **ASAS-Health Index** and change from Week 16 in **FACIT-Fatigue** will be similar to analyses as described for change from Week 16 in total BASDAI.

Analysis of **BASDAI50 response**, **ASAS20** response, **ASAS40** response, and **ASAS partial remission** will be similar to the analyses as described for reduction in ASDAS ≥1.1 from Week 16.

Also summary statistics for secondary efficacy variables 1, 2, 4 and 5 for the patients in Treatment Period 1 who entered Treatment Period 2 will be provided based on the below criteria :

- Patients receiving 150mg (open label) (Enrolled Set)
- Patients receiving randomized 300mg and 150mg (Randomized Set)

- Patients who are responders (Responder Set)
- Patients who are nonresponders (Nonresponder Set)

In addition, the above analysis will be done by TNF-alpha inhibitor status and by visit.

As additional analyses, following will be performed on Full Analysis Set:

1. Descripive summary statistics for change from baseline (Week 0) to all visits in Treatment Period 2 for secondary efficacy variables - total BASDAI, ASAS-Health Index and FACIT-Fatigue, will be provided.
2. Number and percentages of patients for secondary efficacy variables 3 - 6 will also be reported for each treatment group considering baseline (Week 0) to derive the response for Treatment Period 2 and similarly by TNF-alpha inhibitor status only for ASAS20 and ASAS40 response.
3. Line plots of mean change from baseline for secondary efficacy variables – total BASDAI, ASAS-Health Index and FACIT-Fatigue, and line plots displaying responder percentage for secondary efficacy variables 3 – 6, for entire treatment period will be presented from Week 1 to Week 52, considering baseline as Week 0.
4. Descriptive summary statistics for change from baseline (Week 0) in all 6 components of BASDAI will be provided in Treatment Period 1 and 2. Line plots of mean change from baseline (Week 0) for these components will also be presented over entire treatment period (from Week 1 to Week 52).

2.7.3 Handling of missing values/censoring/discontinuations

For secondary efficacy variables 1 and 3 – 6, patients who discontinue prematurely for any reason will be considered nonresponders from the time they discontinued through to Week 52. Also, patients who do not have the required data to compute response (e.g., ASAS components) at the specific time point will be classified as nonresponders.

Secondary efficacy variables 2, 7, and 8, will be analyzed using a mixed-effects model repeated measures (MMRM) which is valid under the missing at random (MAR) assumption. For analyses of these variables, if all post-baseline values are missing then these missing values will not be imputed and the patient will be removed from the analysis of the corresponding variable, i.e., it may be that the number of patients providing data to an analysis is smaller than the number of patients in the FAS.

2.8 Safety analyses

The safety analysis will be performed on Enrolled Set for Treatment Period 1 and on Safety Set for Treatment Period 2.

All listings and tables will be presented for Treatment Period 1, for responders who enter Treatment Period 2, and by treatment group for inadequate responders who are randomized.

The analyses for treatment-emergent adverse events, serious adverse events and risk based on adverse events will be summarized. 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 from 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.

2.8.1 Adverse events (AEs)

The crude incidence of treatment emergent adverse events (TEAEs) will be summarized by primary system organ class (SOC) and preferred term (PT) for Treatment Period 1 and Treatment Period 2.

Treatment-emergent adverse events (TEAEs) are defined as follows:

- For Treatment Period 1, TEAEs are those AEs that started on or after the first dose date of study treatment, or events present prior to the first dose date of study treatment but increased in severity based on preferred term and the earlier of the last dose date in Treatment Period 1 + 84 days or prior to the first dose date in Treatment Period 2.

- For Treatment Period 2, TEAEs are those AEs that started on or after the first dose date of study treatment in Treatment Period 2 and on or before the last dose date + 84 days.

In addition, exposure time-adjusted rates (incidence rate) including 95% confidence intervals will be provided for entire treatment period to adjust for differences in exposure. For the entire treatment period, TEAEs are those AEs that started on or 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 on or before last dose date + 84 days. For summaries over the entire treatment period, patients who switched from secukinumab 150 mg to secukinumab 300 mg will appear in both treatment groups.

Crude incidence rates and exposure-adjusted incidence rates will be graphically presented for all TEAEs and serious TEAEs along with 95% confidence intervals, by system organ class.

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). 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
- serious adverse events
- adverse events leading to discontinuation

A listing of non-treatment emergent adverse events will be provided. These adverse events occurred before the first dose of the study treatment. The crude incidence rate will be provided without treatment information.

Algorithms for date imputations will be provided in Programming Specifications.

For SAEs that occur during screening, a listing will be prepared for all patients screened including screening failures.
A listing of suspected or confirmed SARS-CoV-2 infections will be provided.

For legal requirements of ClinicalTrials.gov, two required tables on TEAEs which are not SAEs with an incidence greater than or equal to 5% and on treatment-emergent SAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT for entire treatment period.

If, for the same patient, several consecutive TEAEs (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 AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.1.1 Adverse events of special interest / grouping of AEs

Not applicable.

2.8.2 Deaths

Separate summaries and listings will be provided for deaths in each treatment period.

2.8.3 Laboratory data

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

Descriptive summary statistics for the change from baseline in Treatment Period 1 and change from Week 16 in Treatment Period 2 to each study visit in respective treatment periods will be presented. These descriptive summaries will be presented by laboratory test and treatment group. Change from baseline (or Week 16) will only be summarized for patients with both baseline (or Week 16) and post-baseline (or post-Week 16) values and will be calculated as:

change from baseline = post-baseline value – baseline value

change from Week 16 = post-Week 16 value – Week 16 value

For urinalysis and urine pregnancy test, data will be listed by treatment and patient.

QuantiFERON TB-Gold test, serum pregnancy test results and HLA-B27 results will be listed at Screening Visit 2, by treatment and patient.

Shift table will be provided for all laboratory variables to compare a patient's baseline laboratory evaluation relative to observed post-baseline values in Treatment Period 1. The reference laboratory ranges will be used to evaluate whether a particular laboratory test value was within reference range, low, or high for each visit value relative to whether or not the baseline value was within reference range, low, or high. The shifts to the most extreme laboratory test value within the treatment period will be presented (including category "high and low"). These summaries will be presented by laboratory test and treatment group. Similar shift tables will be provided for all laboratory variables to compare a patient's Week 16 laboratory evaluation relative to observed post-Week 16 values in Treatment Period 2.

The following laboratory variables will be analyzed with respect to numerical commonterminology criteria for adverse events (CTCAE) grades, given in Table 2-3: hemoglobin (HGB), platelets, white blood cell (WBC) count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glucose.

Table 2-3 CTCAE grades for laboratory variables 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 x 10e9 /L	< 75.0 - 50.0 x 10e9 /L	< 50.0 – 25.0 x 10e9 /L	< 25.0 x 10e9 /L
WBC 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 x 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

LLN = lower limit of normal, ULN = upper limit of normal
*Note: for “creatinine increased” the baseline criteria do not apply

These summaries will be split into hematology and chemistry for study level reports and the pooled summary of clinical safety.
Shift tables will be presented comparing baseline laboratory result (CTCAE grade) with the worst results (expressed in CTCAE grade) during the treatment period analyzed.

Newly occurring or worsening liver enzyme abnormalities will also be summarized based on the event criteria given in Table 2-4 below:

Table 2-4 Liver-related events

Assessment	Criterion
ALT	> 3 x ULN; > 5 x ULN; > 8 x ULN; > 10 x ULN, > 20 x ULN
AST	> 3 x ULN; > 5 x ULN; > 8 x ULN; > 10 x ULN; > 20 x ULN
ALT or AST	> 3 x ULN; > 5 x ULN; > 8 x ULN; > 10 x ULN; > 20 x ULN
TBL	> 1.5 x ULN; > 2 x ULN; > 3 x ULN
ALP	> 2 x ULN; > 3 x ULN; > 5 x ULN
ALT or AST and TBL	ALT or AST > 3 x ULN and TBL > 2 x ULN ALT or AST > 5 x ULN and TBL > 2 x ULN ALT or AST > 8 x ULN and TBL > 2 x ULN ALT or AST > 10 x ULN and TBL > 2 x ULN
ALP and TBL	ALP > 3 x ULN and TBL > 2 x ULN ALP > 5 x ULN and TBL > 2 x ULN
ALT or AST and TBL and ALP	ALT or AST > 3 x ULN and TBL > 2 x ULN and ALP < 2 x ULN (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 > 3 x ULN and TBL > 2 x ULN and ALP ≥ 2 x ULN may not result in severe DILI.

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 = 6.42 × ULN is counted for ALT > 3 × ULN and ALT > 5 × ULN.

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

2.8.3.1 Hematology

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

2.8.3.2 Clinical chemistry

Measured at Screening Visit 2, and Visits 3, 9, 10, 13, 16 and 19, serum chemistry will include glucose, urea, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorous, total protein, albumin, and uric acid.

2.8.3.3 Urinalysis

Urinalysis will be performed at Visits 3, 7, 9, 10, 12, 14, 16 and 19. Dipsticks will be provided by the central laboratory to the sites for local urinalysis assessments. The urinalysis results for standard parameters such as protein, glucose, blood and WBCs will be recorded in the appropriate eCRF page.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

All ECG data at Screening Visit 2 will be listed by treatment group and patient, and abnormalities will be flagged.

2.8.4.2 Vital signs

All vital signs data will be listed by treatment group, patient, and visit. Descriptive summary statistics will be provided by treatment and visit.

The number and percentage of subjects with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided in Table 2-5 below.

Table 2-5 Criteria for notable vital sign abnormalities

Vital sign (unit)	Notable abnormalities
Systolic blood pressure (mmHg)	>= 140 mmHg (hypertension) or < 90 mmHg (hypotension)
Diastolic blood pressure (mmHg)	>=90 mmHg (hypertension) or <60 mmHg (hypotension)
Pulse (bpm)	> 100 bpm (tachycardia) or <60 bpm (bradycardia)

Vital signs will be assessed at Screening Visit 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 and 19 and will include systolic and diastolic blood pressure, pulse rate and body temperature measurements.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

In this section, the details of each PRO is provided. The analysis of the PROs are presented in Section 2.7.

2.11.1 ASDAS and ASDAS response categories

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite index to assess disease activity in AS. The ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score) will be utilized to assess the disease activity status. Parameters used for the ASDAS calculation include spinal pain (BASDAI question 2), the patient's global assessment of disease activity, peripheral pain/swelling (BASDAI question 3), duration of morning stiffness (BASDAI question 6) and C-reactive protein (CRP) in mg/L (Sieper 2009, Lukas 2009).

ASDAS-CRP is calculated in the following way:

$$\text{ASDAS-CRP} = 0.12*\text{Back pain} + 0.06*\text{Duration of Morning Stiffness} + 0.11*\text{Patient Global} + 0.07*\text{Peripheral Pain/Swelling} + 0.58*\text{Ln}(\text{CRP}+1)$$

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

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

- 3.5 between high disease activity and very high disease activity.

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

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

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

ASAS domains:

1. Patient's global assessment of disease activity measured on a numeric rating scale (NRS)
2. Patient's assessment of back pain, represented by either total or nocturnal pain scores, both measured on a NRS (for derivation of response "back pain at any time" will be used from data)
3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by a NRS
4. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI as measured by a NRS

ASAS20

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

ASAS40

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

ASAS partial remission

The ASAS partial remission criteria is defined as a value not above 2 units in each of the domains 1 to 4 on a scale of 10.

[redacted]

[redacted]

[redacted]

2.11.6 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

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

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

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

At least 4 questions should be non-missing to calculate the BASDAI score. Otherwise, BASDAI score will be missing (Haywood et al., 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 are missing and both Q5 and Q6 are not missing, the sum should be divided by 3.

BASDAI50 response is defined as at least a 50% improvement (decrease) in total BASDAI score, as compared to the baseline total BASDAI score.

Note: BASDAI is only assessed at Screening Visit 1 for TNF inhibitor inadequate responders currently on a TNF inhibitor and prior to discontinuation/washout.

2.11.7 ASAS Health Index (ASAS-HI)

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 analyzed based on n=16 or n=15, respectively.

A total score can be analyzed 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 3 missing responses:

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

x = Item summation score

m = Number of missing items

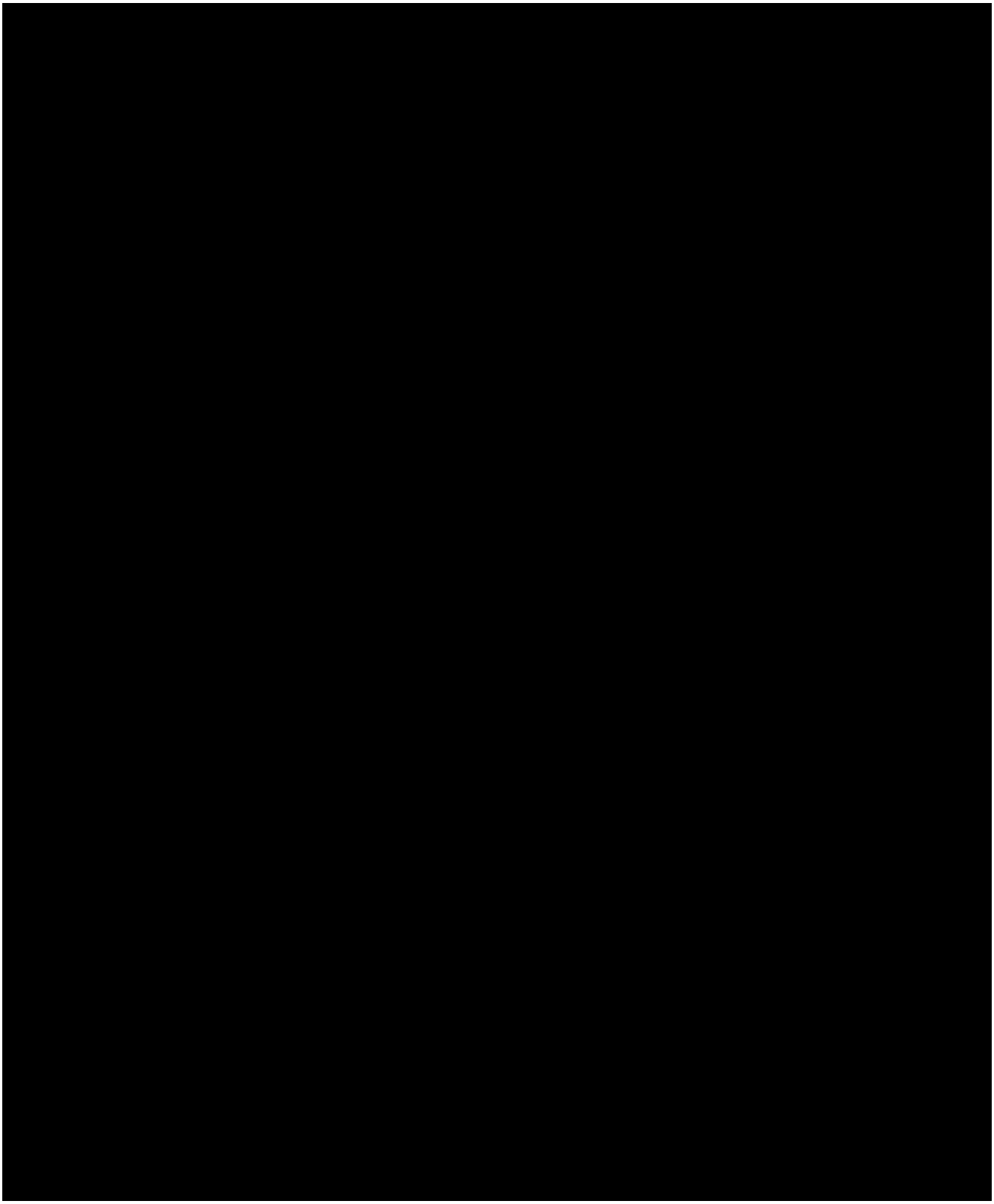
Cases with more than 3 missing responses cannot be allocated a total score.

[redacted]

[redacted]

2.12 Biomarkers

Not Applicable.



[redacted]

[redacted]

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

The FACIT-Fatigue© is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. The purpose of FACIT-Fatigue in this study is to assess the impact of fatigue on patients with AS. Subjects respond to each item on a 5-point Likert-type scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much) based on their experience of fatigue during the past 2 weeks. The scale score is computed by summing the item scores, after reversing those items that are worded in the negative direction. Numbering the questions from 1 to 13, it is evident that questions 7 and 8 are worded in the positive direction (4 indicates a desirable response) and all other questions are worded in the negative directions (4 indicates an undesirable response). Thus, it is necessary to reverse the responses for all questions except questions 7 and 8 (i.e. original response of 0 gets mapped to 4, 1=3, 2=2, 3=1, and 4=0) for scoring purposes.

When there are missing item scores, the scale score will be computed by summing the non-missing item scores, multiplying by 13 (the total number of items in the scale) and dividing by the number of non-missing items (i.e., normalizing the results). The latter rule will be applied only when at least half of the items (seven or more) are non-missing.

FACIT-Fatigue scale score range from 0 to 52, where higher scores represent less fatigue (Cella et al., 2004).

[redacted]

[redacted]

[redacted]

e.

[redacted]

2.14 Interim analysis

No interim analysis is planned.

3 Sample size calculation

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

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

4 Change to protocol specified analyses

For (continuous) secondary efficacy variables 2, 7, and 8 (Section 2.7.1), multiple imputation will not be performed as an additional analysis

For secondary efficacy variables 2, 7, and 8 MMRM will be used for analysis instead of ANCOVA. LOCF will not be used to handle missing data for these variables.

For safety analyses in Treatment Period 1, definition of Enrolled Set will be updated to include patients who received the open-label secukinumab 150 mg.

Randomized Set was deleted.

5 Appendix

This section will be used later for drafting CSR Appendix 16.1.9.

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

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

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
After AE start reference	Partial date indicates AE start date after AE start
Uncertain	Partial date insufficient to determine relationship of AE start date to AE start

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 captured for the study Case1: if AE start date is not equal to AE start reference then do the following:

Relationship	Time imputation
	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		Year
Partial CM Start Date	Not used	MON	YYYY
Treatment Start Date [redacted]	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 start 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

Same as above.

5.1.3.2 Post therapies date imputation

Same as above.

5.1.3.3 Other imputations

Same as above.

5.1.4 Medical history date of diagnosis imputation

Completely missing dates and partially missing end 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

5.4.1 Primary analysis

The primary analysis will be performed comparing treatments with respect to the primary efficacy variable in a logistic regression model with treatment, TNF-alpha inhibitor (naive, inadequate responder) and baseline body weight as explanatory variables.

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

Where TRT = treatment group
TNF = TNF-alpha inhibitor (naive, inadequate responder)
Base_weight = baseline body weight

Logistic regression will be applied to response variables at each visit.

In cases where separation is a concern, e.g., 0% response in one treatment group, an exact logistic regression model will be applied.

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

Multiple Imputation for Primary Efficacy Variable (ASDAS inactive disease response)

A linear regression model will be used to perform multiple imputation (MI) under a missing at random (MAR) assumption. To help preserve the relationship between outcome and covariates within each treatment, a separate model will be run for each treatment. This will also help ensure that the imputation model does not make stronger assumptions on data relations than the analysis model.

To ensure that results can be replicated, the data should be sorted by treatment group, TNF-alpha inhibitor status (naive, inadequate responder), and unique subject ID before running the model. The data should be in horizontal format with one subject per dataset row and should only include one component of the composite variable. Only dataset rows with a non-missing baseline assessment and at least one non-missing post-baseline assessment will be included.

Impute the missing values 500 times (NIMPUTE) with a seed=45706 as shown below:

```
proc mi data= min= max= out=imp minmaxiter=10000000 nimpute=500 seed=45706;
        by trt TNF;
        var weight_Week16 var1_Week16 var1_week20-var1_week52;
        mcmc chain=multiple initial=em;
run;
```

Depending on the component to be imputed, the list of visits in the VAR statement will be adjusted. It will only contain visits where the respective component was planned to be assessed.

<min of scale> and <max of scale> refer to minimum and maximum imputed values and depends on the component:

- All scores measured on NRS: minval=0, maxval=10;
- hs-CRP: minval=0, maxval= (no maximum value)

The imputation of hs-CRP will be based on log(value+1).

If issues with convergence arise:

1. Change Markov Chain Monte Carlo (MCMC) to Fully Conditional Specification (FCS), and check whether it is converged;

2. If both MCMC and FCS do not converge, TNF-alpha inhibitor status should be removed from PROC MI.

This procedure should be repeated separately for each component of the composite variable.

The score as well as ASDAS response can now be calculated based on the complete data. The response rate will be calculated for each imputation and then combined using Rubin's rules.

In order to calculate the response rate for each imputation, PROC FREQ will be used as follows.

Calculate binomial proportion and standard error for each imputation.

```
proc freq data=<ASDAS>;
  by treat visit _imputation_ ;
  tables <response> / binomial (level=2 cl=wilson correct) ;
  ods output BinomialProp=imp_bpr;
run;
```

Transpose the dataset for subsequent use with PROC MIANALYZE.

```
proc transpose data=imp_bpr out=imp_trs(drop=_name_) ;
  by treat visit _imputation_ ;
  var nvalue1; id name1; idlabel label1;
run;
```

Apply LOGIT transformation: y=log(p/(1-p)) and std. err. transformation: <new se> = se/(p*(1-p))

```
data logit;
  set imp_trs(rename=(_bin_=p e_bin=se));
  by treat visit _imputation_ ;
  lmean=log(p/(1-p));
  lse=se/(p*(1-p));
run;
```

The transformed binomial proportion estimates and standard errors are combined by applying Rubin's rules for multiple imputed data sets.

```
proc mianalyze data=logit;
  by treat visit ;
  modeleffects lmean;
  stderr lse;
  ods output ParameterEstimates=logitres;
run;
```

The combined data should be transformed back using the following formula: p=1/(1+exp(-y))

```
data miexpres;
  set logitres;
  by treat visit ;
  resti = 1/(1+exp(-estimate));
  rlow = 1/(1+exp(-lclmean));
  rupp = 1/(1+exp(-uclmean));
run;
```

If all responses are imputed the same as 0 (or 1) for all imputation datasets for a specific treatment or subgroup, then the between-imputation-variation will be zero. The combined final response rate for the specific treatment would be presented as seen in any of the imputed datasets together with 95% confidence interval from Wilson's method (as obtained from PROC FREQ).

The following steps will be performed to handle special cases:

- If after imputation all responses (observed + imputed) are the same either 0 or 1 for all imputation datasets for a specific treatment, it will not be possible to perform a logit transformation and the response rate (0% or 100%) for these cases will be presented together with the 95% CI from Wilson's method (as obtained from PROC FREQ).
- If after imputation the average response rate is the same across all imputed datasets (but not 0 or 1), there is no between-dataset variation and Rubin's rules cannot be applied. Instead the average response will be used with 95% CI from Wilson's method (as obtained from PROC FREQ).

The odds ratio will be derived using GENMOD for each imputation, then combined using Rubin's rules again.

```
proc genmod data = acr20_mi descending;
        by avisitn _imputation_;
        class trt_ TNFRESN ;
        model aval = trt_ TNFRESN  weight  / link=logit dist=bin;
        lsmeans trt_ / diff;
        estimate 'AIN457 150 mg vs AIN457 300 mg' trt_ 1 -1;
        estimate 'AIN457 150mg mg vs Placebo' trt_ 0 1 -1;
        ods output Estimates=imp_est;
run;
proc mianalyze data=imp_est;
        by avisitn trt_ ;
       modeleffects LBetaEstimate;
        stderr StdErr;
        ods output ParameterEstimates=_res;
run;
```

5.4.2 Key secondary analysis

Not applicable.

5.4.3 Secondary analysis

Binary variables will be analyzed using the logistic model; code is described above (Section 5.4.1).

For continuous secondary [redacted] efficacy variables, MMRM approch will be used with treatment, visit, and TNF-alpha inhibitor status as factors, Week 16 score and Week 16 weight as covariates, and treatment-by-visit and Week 16 score-by-visit as interaction terms.

The following SAS code will be applied :

```
Proc mixed data=<dataset> order=internal method = reml;
class visit TNF-alpha ;
model Change_score = Wk16_score TNF-alpha Wk16_weight avisit trt*avisit
Wk16_score*avisit / s ddfm=kr;
repeated visit / type=un subject=USUBJID;
lsmeans visit / cl;
run;
```

where;

Wk16_score = Week 16 score

avisit = Analysis visit (Week 20, 24,28, 32, 36, 40, 44, 48 and 52)

TNF-alpha = TNF-alpha status

weight = subject weight

USUBJID= Subject ID

Change_score = Change in score of specified variable from Week 16 to each post-baseline visit

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 in the following order until convergence is achieved: weight, blscore*visit, TNF-alpha.

5.4.5 Exposure-adjusted incidence rate and 100*(1-α)% confidence interval

It will be assumed that for each of n subjects in a clinical trial the time t_j (j=1,...,n) to the first occurrence of a certain event is observed, or if the event was not experienced, the (censored) time to the end of the observation period. The total exposure time will be the total number of days with an actual dose greater than zero summed up over all patients, and then divided by 365.25 days. Incidence rate will be calculated per 100 patient years.

The sequence of first occurrences of an event will be modeled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as λ =D/T, where T = $\sum t_j$, (j=1,...,n) and D is the number of subjects with at least one event. Conditionally on T, an exact 100*(1- α)% confidence interval for a Poisson variable with parameter θ T and observed value D can be obtained based on (Garwood,1936), from which an exact 100*(1- α)% confidence interval for D/T will be derived as follows (Sahai and Anwer, 1993; Ulm, 1990):

Lower confidence limit:

$$L = \frac{0.5c_{\alpha/2,2D}}{T} \text{ for D>0, 0 otherwise,}$$

Upper confidence limit :

$$U = \frac{0.5c_{1-\alpha/2,2D+2}}{T}$$

where $c_{\alpha,k}$ is the α th quantile of the Chi-square distribution with k degrees of freedom.

5.4.6 Crude incidence and 100*(1-α)% confidence interval

For n subjects, each at risk to experience a certain event with probability π, the crude incidence is estimated as p=x/n, where x is the number of subjects with the event.

Absolute and relative frequencies will be displayed as well as 95% confidence interval for the relative frequency based on the score method including continuity correction (Newcombe 1998).

With z as (1- α /2)-quantile of the standard normal distribution (SAS: z=PROBIT(1-alpha/2), n as total number of subjects (i.e. number of subjects in the denominator), and p as estimated crude incidence (number of subjects with event / n) it is $q = 1-p$.

Then the lower limit is:

$$L = 100 \times \max\left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - 1/n + 4p(nq+1)}}{2(n+z^2)}\right)$$

and the upper limit is:

$$U = 100 \times \min\left(1, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - 1/n + 4p(nq-1)}}{2(n+z^2)}\right).$$

In addition, if L > p x 100 then L = p x 100 and if U < p x 100 then U = p x 100.

5.5 Rule of exclusion criteria of analysis sets

Table 5-1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of deviation	Exclusion in analyses	Severity code
D01	Patient met one or more of the Discontinuation of Study Drug criteria but study drug was not discontinued	Include in everything	0
D02	Patient voluntarily withdrew consent. However, still continuing in the study.	Exclude from everything	9
E01	Patient enrolled with total ankylosis of the spine	Include in everything	0
E02	Patient used other investigational drugs within 5 half-lives of enrollment, or within 4 weeks before the Baseline Visit, whichever is longer	Include in everything	0
E03	Patient enrolled with history of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes	Include in everything	0
E04	Patient enrolled with Chest x-ray, CT scan, or chest magnetic resonance imaging (MRI) with evidence of ongoing infectious or malignant process, obtained within 3 months prior to screening and evaluated by a qualified physician	Include in everything	0
E05	Patient enrolled with previous exposure to secukinumab or any other biologic drug directly targeting IL-17, IL-12/23, or the IL-17 receptor, or any other biologic immunomodulating agent, except those targeting TNF α	Include in everything	0
E06	Patient who took more than one anti-TNF α agent	Include in everything	0
E07	Patient took any intramuscular or intravenous corticosteroid injection within 2 weeks before baseline	Include in everything	0
E08	Patient took any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before baseline	Include in everything	0
E09	Patient enrolled whose previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)	Include in everything	0
E10	Patient using high potency opioid analgesics (e.g., methadone, hydromorphone, morphine)	Include in everything	0
E11	Patient enrolled with active systemic infections during the last two weeks	Include in everything	0

Deviation ID	Description of deviation	Exclusion in analyses	Severity code
	(exception: common cold) prior to baseline		
E12	Patient enrolled with active ongoing inflammatory diseases other than AS that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease or uveitis	Include in everything	0
E13	Patient enrolled with underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy	Include in everything	0
E14	Patient has significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension, congestive heart failure (New York Heart Association status of class III or IV), uncontrolled diabetes, or very poor functional status unable to perform self-care	Include in everything	0
E15	Patient enrolled with history of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria: Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be rechecked once more as soon as possible, and in all cases, at least prior to enrollment/baseline, to rule out lab error	Include in everything	0
E16	Patient enrolled with serum creatinine level exceeding 2.0 mg/dL (176.8 umol/L) at screening	Include in everything	0
E17	Patient enrolled with Screening total WBC count < 3,000/uL, or platelets < 100,000/uL or neutrophils <1,500/uL or hemoglobin < 8.5 g/dL (85 g/L)	Include in everything	0
E18	Patient enrolled with Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening	Include in everything	0

Deviation ID	Description of deviation	Exclusion in analyses	Severity code
E19	Patient enrolled with history of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)	Include in everything	0
E20	Patient enrolled with other clinically significant conditions (not associated with the study indication) which in the judgement of the investigator might interfere with the assessment of this study, or puts the patient at increased risk	Include in everything	0
E21	Patient enrolled with inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)	Include in everything	0
E22	Patient enrolled with inability or unwillingness to receive injections with the PFS	Include in everything	0
E23	Patient enrolled with any medical or psychiatric condition which, in the Investigators opinion, would preclude the participant from adhering to the protocol or completing the study per protocol	Include in everything	0
E24	patient enrolled, and had donated or loss of 400 mL or more of blood within 8 weeks before baseline	Include in everything	0
E25	patients enrolled and had a history or evidence of ongoing alcohol or drug abuse, within the last 6 months before baseline	Include in everything	0
E26	Patient enrolled and knew he/she will be unable to complete 1 year of study treatment period	Include in everything	0
E27	Patient enrolled and has received Administration of live vaccines during the study period or 6 weeks prior to baseline	Include in everything	0
E28	Patient enrolled and has History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of >= 5 mm	Include in everything	0

Deviation ID	Description of deviation	Exclusion in analyses	Severity code
E28A	Patient enrolled with a positive central laboratory TB blood screening test and did not have further work up (according to local practice/guidelines) establishing conclusively that the patient has no evidence of active tuberculosis.	Include in everything	0
E28B	Patient had latent tuberculosis established, and then treatment was not initiated according to local country guidelines.	Include in everything	0
E29	Patient is enrolled and Pregnant or nursing (lactating) women where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test	Include in everything	0
E30	Patient was enrolled and Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, and did not use highly effective methods of contraception during dosing and for 16 weeks after stopping of study medication.	Include in everything	0
I01	Patient was not able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study assessment is performed	Include in everything	0
I02	Patient was not male or non-pregnant, non-lactating female patients at least 18 years of age	Include in everything	0
I03	Patient did not have a diagnosis of moderate to severe AS with prior documented radiologic evidence (x-ray or radiologist's report) fulfilling the Modified New York criteria for AS	Include in everything	0
I04	Patient did not have active AS assessed by total BASDAI of >= 4 (NRS of 0-10) at baseline	Include in everything	0
I05	Patient did not have spinal pain as measured by BASDAI question #2 of >= 4 (NRS of 0-10) at baseline	Include in everything	0
I06	Patient did not have total back pain of >= 4 on a NRS of 0-10 at baseline	Include in everything	0
I07	Patient was not taking NSAIDs at the maximum tolerated dose for at least 4 weeks prior to their Baseline Visit, with an inadequate response or for less than	Include in everything	0

Deviation ID	Description of deviation	Exclusion in analyses	Severity code
	4 weeks if withdrawn for intolerance, toxicity or contraindications		
I08	Patient was regularly taking NSAIDs (including COX-1 or COX-2 inhibitors) as part of their AS therapy was not on a stable dose for at least 2 weeks before their Baseline Visit	Include in everything	0
I09	Patient was on a TNFα inhibitor (not more than one) but did not experience an inadequate response to previous or current treatment given at an approved dose for at least 3 months prior to baseline or did not experience intolerance upon administration of an anti-TNFα agent	Include in everything	0
I10	Patient has been previously on a TNFα inhibitor and did not have appropriate wash-out period prior to a week before their Baseline Visit	Include in everything	0
I11	Patients taking MTX (<= 25 mg/week), sulfasalazine (<= 3 g/day), or leflunomide (<=20 mg/day) are allowed to continue their medication and must have taken it for at least 2 months and have to be on a stable dose for at least 4 weeks prior to baseline.	Include in everything	0
I12	Patients on MTX must be on a stable folic acid supplementation before their Baseline Visit.	Include in everything	0
I13	Patient was on a DMARD other than MTX, sulfasalazine or leflunomide and did not discontinue the DMARD 4 weeks prior to baseline	Include in everything	0
I14	Patient took systemic corticosteroids and was not on a stable dose of <= 10 mg/day prednisone or equivalent for at least 2 weeks before baseline	Include in everything	0
M01	Patient had concomitant intake of a prohibited medication as outlined in protocol after randomization and remained on study treatment	Include in everything	0
M02	Patient has used live virus vaccines during the study after the baseline visit. However still patient is part of study.	Include in everything	0
M03	Failure to initiate / modify concomitant medication doses according to protocol	Include in everything	0
O01	Site is not compliant to ICH GCP at any time in the study	Include in everything	0
O02	Deficient informed consent or any other process documentation at any time in the study.	Include in everything	0

Deviation ID	Description of deviation	Exclusion in analyses	Severity code
O03	Failure to perform key study efficacy procedures for example, ASDAS, BASDAI, ASAS20, ASAS40, ASAS partial remission, ADAS-Health Index, or FACIT	Include in everything	0
O04	Failure to perform safety procedure such as vitals, central labs, ECG, and pregnancy.	Include in everything	0
[redacted]			
O06	Any other protocol deviation or observation not specified in the protocol deviations list.	Include in everything	0
O07	Missed visit due to COVID-19	Include in everything	0
O08	Visit done outside of study site due to COVID-19	Include in everything	0
O09	Assessment / procedure changed due to COVID-19	Include in everything	0
O10	Visit conducted out of window for week 12, week 16, or week 52 due to COVID-19	Include in everything	0
D03	Study/Treatment Discontinuation due to COVID-19	Include in everything	0
S01	Failure to return or failure to follow sponsor/institution for returning unused study medication	Include in everything	0
S02	Improper storage and/or accountability of study medication	Include in everything	0
S03	Incorrect study medication stock used/dispensed	Include in everything	0
S04	Improper procedure followed for Emergency Breaking of Assigned Treatment Code	Include in everything	0
S05	Any incorrect route of administration of study drug at any time during the study, per protocol	Include in everything	0
S06	Missed study drug administration at any time in the study.	Include in everything	0
S07	Patient received more injections than prescribed by protocol.	Include in everything	0
S08	Incorrect ASDAS domain [redacted] result entered into IRT at Baseline, Week 12 or Week 16	Include in everything	0
S09	Drug supply method changed due to COVID-19	Include in everything	0

Table 5-2 Analysis set exclusions based on codes

Analysis set	Codes that cause a subject to be excluded
SAF	5, 7, 9
FAS	4, 7, 8, 9
ENR	1, 9
Responder Set	2, 8, 9
Non-Responder Set	6, 8, 9

Table 5-3 Code text

Code	Code text
0	Include in everything
1	Exclude from Enrolled Set
2	Exclude from Responder Set
3	Exclude from Randomized Set (RAN)
4	Exclude from Full Analysis Set (FAS)
5	Exclude from Safety Set (SAF)
6	Exclude from Nonresponder Set
7	Exclude from FAS and SAF
8	Exclude from FAS, Responder Set, Randomized Set and Nonresponder Set
9	Exclude from everything

5.6 Evaluation algorithm for ASDAS inactive disease status

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

- Responders: Patients achieving ASDAS inactive disease (total score < 1.3) at **both** Week 12 and Week 16 and who do achieve a decrease (improvement) from baseline in total ASDAS score at both Week 12 and Week 16.
- Inadequate responders: Patients not achieving ASDAS inactive disease at Week 12 and Week 16 (i.e., not achieving total score < 1.3), but who do achieve decrease (improvement) from baseline in total ASDAS score at Week 12 and Week 16.
- Non-responders: Patients who exhibit no change or an increase (worsening) from baseline in total ASDAS score at **either** Week 12 **or** Week 16.

Patient	Baseline ASDAS	Week 12 ASDAS <1.3	Week 16 ASDAS < 1.3	Week 12 ASDAS < Baseline	Week 16 ASDAS < Baseline	Responder status	Definition
Patient 1		Yes	Yes			Responder	1
Patient 2	?	No	No	Yes	Yes	Inadequate	2
Patient 3	?	Yes	No	Yes	Yes	Inadequate	2
Patient 4	?	No	Yes	Yes	Yes	Inadequate	2
Patient 5	?	No	No	Yes	No	Non-responder	3
Patient 6	?	No	No	No	Yes	Non-responder	3
Patient 7	?	No	No	No	No	Non-responder	3
Patient 8	?	Yes	No	Yes	No	Non-responder	3
Patient 9	?	Yes	No	No	Yes	Non-responder	3
Patient 10	?	Yes	No	No	No	Non-responder	3
Patient 11	?	No	Yes	Yes	No	Non-responder	3
Patient 12	?	No	Yes	No	Yes	Non-responder	3
Patient 13	?	No	Yes	No	No	Non-responder	3

SAS program logic:

Do;

If ASDAS12 < 1.3 and ASDAS16 <1.3

then RESPONSE = “Responder”;

Else if ASDAS12 <ASDAS0 and ASDAS16 < ASDAS0

then RESPONSE = “Inadequate”;

Else RESPONSE = “Non-responder”;

End;

6 References

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