NOVARTIS

Clinical Development Secukinumab (AIN457)

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An extension study to evaluate the sustainability of clinical benefits, safety and tolerability of secukinumab in patients with active Ankylosing Spondylitis

RAP Module 3 Week 260 – Detailed Statistical Methodology

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Version	Date	Changes

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List of tables

List of abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase/ Glutamic Pyruvic Transaminase/ GPT
AS	Ankylosing Spondylitis
ASAS	Assessment of Spondyloarthritis International Society criteria
[redacted]	[redacted]
AST	Aspartate Aminotransferase/ Glutamic Oxaloacetic Transaminase/ GOT
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
CI	Confidence Interval
[redacted]	[redacted]
CRO	Contract Research Organization
DMC	Data Monitoring Committee
ECG	Electrocardiogram
[redacted]	[redacted]
[redacted]	
FAS	Full Analysis Set
GGT	Gamma Glutamyl Transferase
IA	Interim Analysis
IL	Interleukin
IRT	Interactive Response Technology
[redacted]	[redacted]
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
[redacted]	[redacted]
PDS	Programing Data Specifications
PCS	Physical Component Summary
[redacted]	[redacted]
[redacted]	[redacted]
RA	Rheumatoid Arthritis

SAE	Serious Adverse Event
SCR	Screening
[redacted]	[redacted]
TNF	Tumor Necrosis Factor
TNFα-IR	TNFα Inhibitor Incomplete Responders
ULN	Upper Limit of Normal
VAS	Visual Analog Scale

1 Introduction

Data will be analyzed by Novartis according to the data analysis section 9 of the study protocol. The statistical methodology is described below and any deviations from the protocol are documented. Additional detailed information regarding the analysis methodology is contained in the Appendix section.

2 Changes to statistical methods planned in the protocol

MMRM modeling will be employed for all hierarchy continuous variables. Multiple imputation will be performed to impute the missing values [redacted] components in order to analyze the [redacted] inactive disease.

3 Study objectives

3.1 Primary objectives

The primary objective is to evaluate the sustainability of subject benefits as quantified by the ASAS20 (Assessment of SpondyloArthritis International Society criteria) in the whole study population during long-term (Week 260) treatment with secukinumab 75 and 150 mg provided as prefilled syringes.

3.2 Secondary objectives

1. To evaluate the sustainability of subject benefits in subjects with active AS as quantified by the ASAS40 response during long-term treatment with secukinumab 75 or 150 mg.
2. To evaluate the overall safety and tolerability of secukinumab in subjects with active AS.

[redacted]

4 Data presentation

Data analyses will be presented by treatment groups. For efficacy analysis the assigned and actual treatment will be displayed.

Unless otherwise stated, summary tables/figures/listings will be on all subjects included in the population under consideration.

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies.

For categorical or binary variables, the number and percent of subject in each category will be presented. The p-values, if presented, will be two-sided unless otherwise specified, and 95% CIs will be provided as appropriate.

In general, efficacy data from the extension study period will be reported for clinical study report (CSR) and publication(s). Efficacy tables and figures corresponding to the hierarchy assessments (e.g. ASAS20/40 responder analysis) will be presented from Week 1 in the core study up till the end of reporting period in the extension trial.

No formal hypothesis testing will be done. Hence, the p-values and CIs provided should be considered as exploratory only.

Safety data from core and extension studies will be reported cumulatively for CSR and publication(s). Placebo safety data from core will be reported only in the listings. For subjects who switched from placebo to secukinumab in core, their data prior to switch will not be reported.

All listings will be presented by treatment groups. All listings but the listings of deaths, non-fatal serious adverse events and adverse events requiring treatment discontinuation will display the placebo group followed by the indication of responder or non responder.

5 Subjects and treatments

5.1 Analysis Sets

The following analysis sets will be used for the data analysis:

Extension Full Analysis Set (extension FAS): The extension FAS will be comprised of all subjects enrolled in the extension study.

(In this document extension FAS is referred to as FAS).

Of note, FAS will comprise only the subjects from extension whereas safety set will include from core or extension, safety set will be larger than FAS.

Up-titration Subset: The up-titration subset will be comprised of all subjects from the extension FAS set who received at least one dose of the up-titration dose.

[redacted]

Safety set: The safety set includes all subjects enrolled in the core study who took at least 1 dose of study treatment during the core study. Subjects will be evaluated according to treatment received.

5.2 Treatment groups

Unless otherwise specified, the summaries will be performed by the treatment sequence.

- Efficacy:
  - AIN457 10 mg/kg - 75 mg -150 mg
  - AIN457 10 mg/kg - 150 mg
  - Placebo - AIN457 75 mg – 150 mg
  - Placebo - AIN457 150 mg
  - Any AIN457 75 mg
  - Any AIN457 150 mg

After week 52 the combination of assigned treatments will also be shown as follows:

- AIN457 75 mg & Placebo - AIN457 75 mg
- AIN457 150 mg & Placebo - AIN457 150 mg

Tables on MMRM or MI estimates will be summarized only for the AIN457 10 mg/kg - 150 mg originally randomized group.

- Safety
  - Any AIN457 75 mg
  - Any AIN457 150 mg
  - Any AIN457

Placebo treatment group will be displayed only in safety listings and in in-tex safety tables.

6 Subgroup definitions

The primary endpoint(s) and secondary endpoints will be evaluated by TNF-alpha inhibitor status.

7 Assessment windows, baseline and post baseline definitions, missing data handling

Baseline and post-baseline definitions

In general [redacted], a *baseline* value refers to the last measurement made 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 X-ray, a baseline value is the last measurement prior to dosing if available, or the first value within 30 days post dosing if no other value is available prior to dosing.

[redacted]

For post baseline visit -windows during the core study the following applies (unless otherwise specified):

For quantitative variables, the closest to the actual visit is chosen (if two assessment have the same distance, then the earlier now will be chosen)/

For qualitative variables, the worst record is selected. It is noted that in the analysis performed, worst case is always well defined (e.g., for urine protein values “+” and “++” the worse case is defined as “++”).

Analysis 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. The analysis visit windows and rules for dealing with multiple measurements within the windows are described in Section 19.1.

For visits that occur after week 104, the recorded nominal visit data will be considered.

8 Subject disposition, background and demographic characteristics

8.1 Subject disposition

The number of subjects enrolled in the extension was presented at the will be presented. The number and percentage of subjects in the FAS who completed the study and who discontinued the study prematurely (including the reason for discontinuation) will be presented for each treatment group and all subjects.

For the week 260 final DBL, for each protocol deviation (PD), the number and percentage of subjects for whom the PD applies will be tabulated.

8.2 Background and demographic characteristics

Demographics and Baseline characteristics for FAS as well as for the subjects in FAS that up-titrated will be displayed. The following common background and demographic variables will be analyzed for these subjects:

Continuous variables:

- Age (which is derived from date of birth and the screening assessment date)
- Height
- Weight
- Body mass index (BMI) = (body weight in kilograms) / (height in meters)^2

Categorical variables:

- Age categories (<65 years, 65 years and older, 75 years and older)
- Gender
- Race
- Ethnicity
- Weight (<70 kg, 70-90 kg, >90kg)
- Smoking status at baseline

The following disease specific baseline characteristics and history of disease will be summarized as well:

Patient's global assessment of disease activity and other ASAS components, [redacted], prior use of TNF-alpha inhibitors, number of prior TNF alpha inhibitors, use (yes/no) and separate dose of methotrexate (mg/week), sulfasalazine (g/day) and systemic corticosteroids (mg/day) at randomization, time since first diagnosis of AS (years), modified New York criteria for AS, HLA-B27, [redacted]

[redacted]

Summary statistics will be presented for continuous variables for each treatment group and for all subjects (total) in the FAS as well as for the FAS patients who up-titrated during the study. The number and percentage of subjects in each category will be presented for categorical variables for each treatment and all subjects (total) in the FAS.

9 Medical history

Any condition entered on the *Relevant medical history / current medical conditions* CRF is to be coded using the MedDRA dictionary. Summaries by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary were already presented in the SAF population during the core study. The same stands for summaries for cardiovascular medical history and Ankylosing Spondylitis medical history.

Chest x-ray (screening) results will not be listed.

10 Study medication

The analysis of study treatment data will be based on the safety set. The number of active injections will be summarized by treatment group. The duration of exposure to study treatment will also be summarized by treatment group. In addition, the number and percentage of subjects with cumulative exposure levels (e.g. any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, ≥ 8 weeks, etc.) will be presented.

Duration of exposure will be calculated as time from first dose of study treatment in core to the minimum of (last dose of the treatment + 84 days) and (last visit date). For subjects who discontinue, this will be the subject's last visit in the corresponding treatment period.

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

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

The analyses of duration of exposure described above will be done for the entire study treatment period.

11 Concomitant medication

Concomitant medication in extension

Concomitant medications in extension will be summarized by treatment dose. Any medication given at least once between the start of the first dose in this extension trial and 84 days after the last study visit in the extension study will be a concomitant medication, including those which were started before Week 104E1 and continued into the extension study 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 concomitant non-drug therapies (e.g. prior surgeries) and procedures will be summarized by primary system organ class and MedDRA preferred term.

Prior surgeries and procedures are defined as surgeries and procedures executed prior to the first study dose. Any surgeries and procedures started between the day of the first dos of study treatment and within 84 days after the last dose will be concomitant surgeries and procedures, including those which were stared pre-baseline and continued into the period where study treatment is administered.

The number and percentage of subjects receiving prior and concomitant ankylosing spondylitis therapy will be presented by 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 psoriatic arthritis therapies previously.

Data will be analyzed on SAF.

Concomitant medication in core or extension

Concomitant medications data collected in core and extension will be combined together. Data for concomitant medications for core are collected in core study and the same will be used.

Any medication given at least once between the start of the first dose in core trial and the date of the last study visit in the extension trial will be summarized. Data will be analyzed on safety set.

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

12 Efficacy evaluation

12.1 Description of efficacy variables

Assessment of Spondyloarthritis International Society criteria (ASAS) response criteria

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

Main ASAS domains:

1. Patient's global assessment of disease activity measured on a VAS scale
2. Patient's assessment of back pain, represented by either total or nocturnal pain scores, both measured on a VAS scale. *For ASAS response analyses, the total back pain will be used.*
3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS scale

4. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI as measured by VAS scale (at least one question is needed)

Additional assessment domains:

5. [redacted]
6. [redacted]

[redacted]

ASAS components

Patient's global assessment of disease activity (VAS)

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

Patient's assessment of total inflammatory back pain and nocturnal back pain intensity (VAS)

The patient's assessment of inflammatory back pain will be performed using a 100 mm VAS ranging from no pain to unbearable pain, after the question "*Based on your assessment, please*

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

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 scales gives the BASFI score – a value between 0 and 10.

In the case that some of the BASFI questions are missing then the average of the non-missing items will be utilized (Braun 2009, van Tubergen 2001)

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The gold standard for measuring and evaluating disease activity in AS is the BASDAI. The BASDAI consists of a 0 through 10 scale (0 being no problem and 10 being the worst problem), 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. The mean of questions 5 and 6 is added to the score from questions 1-4. If one of questions 5 or 6 is missing, then the non-missing one should be added. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score. Scores of 4 or greater suggest suboptimal control of disease, and subjects with scores of 4 or greater are usually good candidates for either a change in their medical therapy or for enrollment in clinical trials evaluating new drug therapies directed at AS. BASDAI is a quick and simple index taking between 30 secs and 2 mins 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 are missing and both Q5 and Q6 are not missing the sum should be divided by 3.

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. maximal intermalleolar distance (cm)
5. cervical rotation angle (°)

Additionally, the following assessments should be taken:

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

The assessments *A* of the first five components into the scores *S* using the equations are given in Table 12-1 (van der Heijde et al, 2013). All 5 components should be non-missing to calculate BASMI.

Table 12-1 Equations for the conversion of the assessments A into scores S for the five components of the BASMI linear

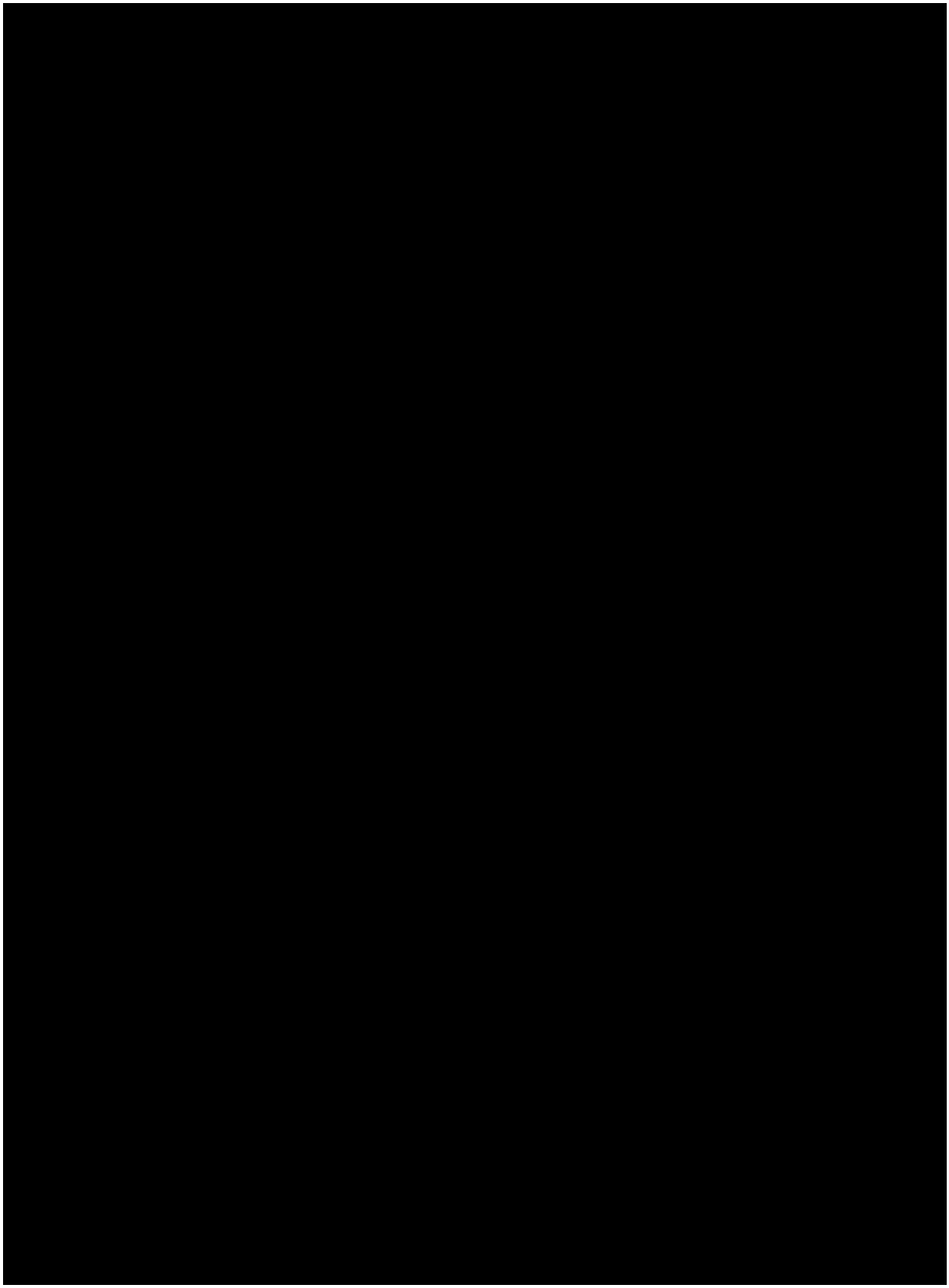
	S = 0 if	Between 0 and 10	S = 10 if
Lateral lumbar flexion* (cm)	A ≥ 21.1	S = (21.1 – A)/2.1	A ≤ 0.1
Tragus-to-wall distance* (cm)	A ≤ 8	S = (A – 8)/3	A ≥ 38
Lumbar flexion (modified Schober) (cm)	A ≥ 7.4	S = (7.4 – A)/0.7	A ≤ 0.4
Intermalleolar distance (cm)	A ≥ 124.5	S = (124.5 – A)/10	A ≤ 24.5
Cervical rotation angle*(°)	A ≥ 89.3	S = (89.3 – A)/8.5	A ≤ 4.3

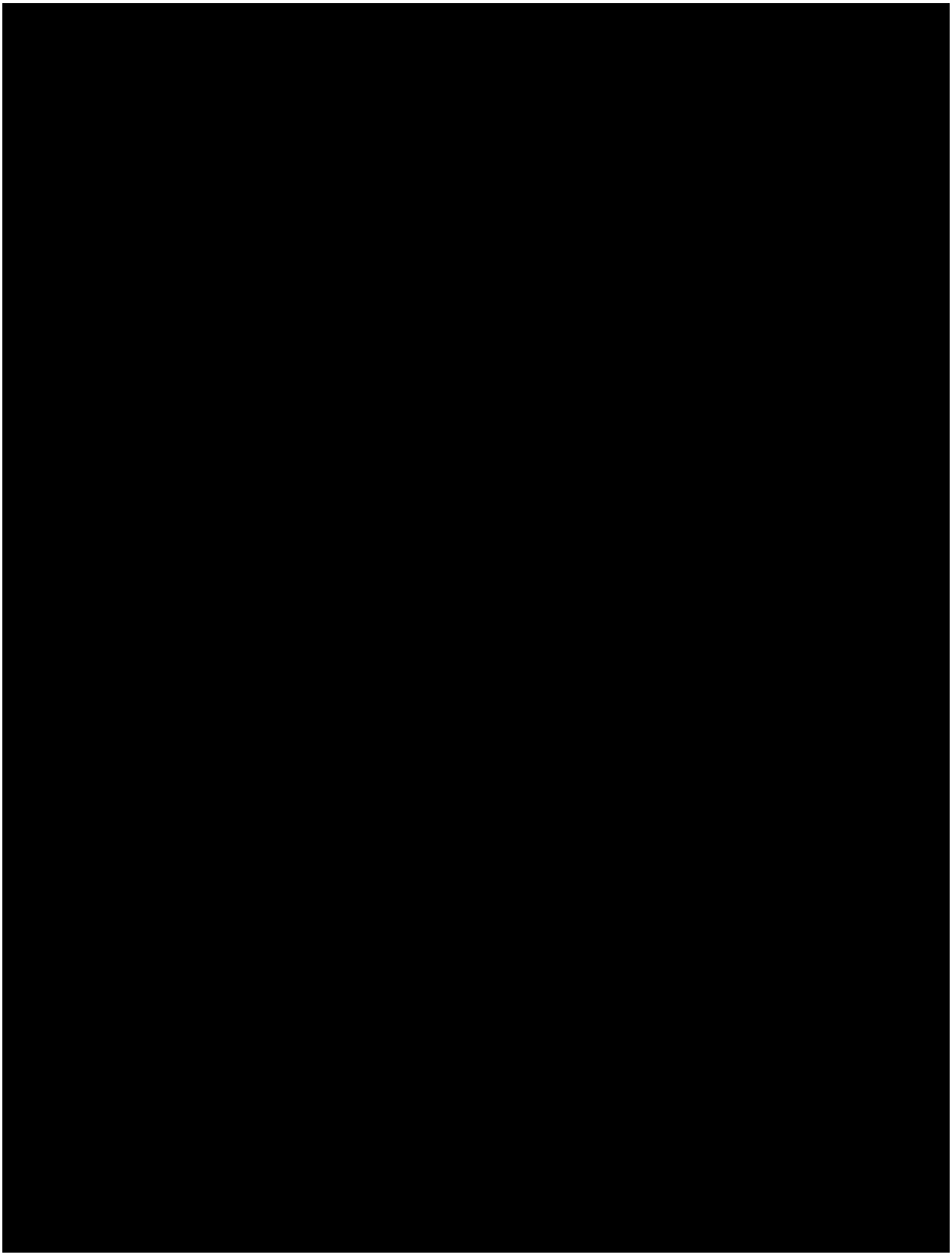
* For lateral lumbar flexion, tragus-to-wall distance, and cervical rotation the average of right and left should be taken.

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.

[redacted]





[redacted]

12.3 Handling of missing data

Missing data

Analysis of study data will be based on the observed data. In addition to the observed data approach, multiple imputation technique will be employed for the following binary variables: ASAS20, ASAS40, Analysis will be limited to the higher originally randomized dose (AIN457 10 mg/kg - 150 mg)

For analyses of these parameters, if all post baseline values are missing then these missing values will not be imputed and this subject will be removed from the analysis of the corresponding variable, i.e. it might be that the number of subjects providing data to an analysis is smaller than the number of subjects in the FAS.

mixed model repeated measures (MMRM) will be fitted assuming random missingness to assess the durability of secukinumab effect. The explanatory variables will be baseline score, weight,

TNFα status, analysis visit, and analysis visit by baseline score. An unstructured correlation matrix will be used thus allowing adjustment for correlations between time points within subjects. This analysis will be done on the entire treatment period for the AIN457 10 mg/kg - 150 mg treatment arm.

13 Analysis of the primary variable(s)

13.1 Variable(s)

The primary efficacy variable is the clinical response to treatment according to the ASAS20 over time up to Week 260. The analysis of the primary variable will be based on the FAS subjects.

13.2 Statistical model, hypothesis, and method of analysis

No formal hypotheses are proposed for this study. The proportion of subjects meeting the ASAS20 will be descriptively summarized for each treatment over time from week 1 in core study onwards and treatments will be compared by providing 95% CIs for the proportion of patients responding to treatment according to the ASAS20 criteria. Results will be presented for the FAS, as well as subgroups by TNFα status (naive or IR).

13.3 Supportive analyses

Sensitivity analyses will be performed by using multiple imputation for missing assessments for ASAS20/40 to assess the robustness of missing data handling.

14 Analysis of secondary [redacted] variables

14.1 Efficacy variables

Secondary [redacted] variables include:

- the proportion of subjects achieving ASAS40

[redacted]

[redacted]

For binary variables, the proportion of responders along with the 95% CI will be presented by groups according to the treatment sequence over analysis visits. For continuous variables, the change from core baseline will be summarized.

Results will be presented for the FAS, as well as subgroups by TNFα status (naive or IR) for the following variables: ASAS40, [redacted]

Graphical representation (line plots) regarding the response over time for the following measures will be provided in the observed data: ASAS20/40, [redacted] will also be graphically illustrated. The above mentioned figures will show the originally randomized AIN457 treatment groups.

Cumulative probability plots will be employed to display the change from baseline to week 208 illustrating the progression of subjects after 4 years [redacted]

Additional figures as in line plots, illustrating the up-titration effect of treatment will be created for the following parameters: ASAS20/40, [redacted]

ASAS20

The ASAS Response Criteria (ASAS20) is defined as an improvement of ≥20% and ≥1 unit on a scale of 10 in at least three of the four main domains and no worsening of ≥20% and ≥1 unit on a scale of 10 in the remaining domain.

The percentage of subjects experiencing ASAS20 response, followed by the respective 95% CI, will be presented be treatment sequence up to week 260 based on the observed data. The respective summaries will also be provided by TNF-α IR status.

Additional analysis will be based on the imputed responses only for the AIN457 150 mg group.

The percentage of subjects (and the 95% CI) experiencing ASAS20 response after up-titration will be presented in separate tables (observed data). Patients who had at least 1 dose of the up-titrated dose will be included.

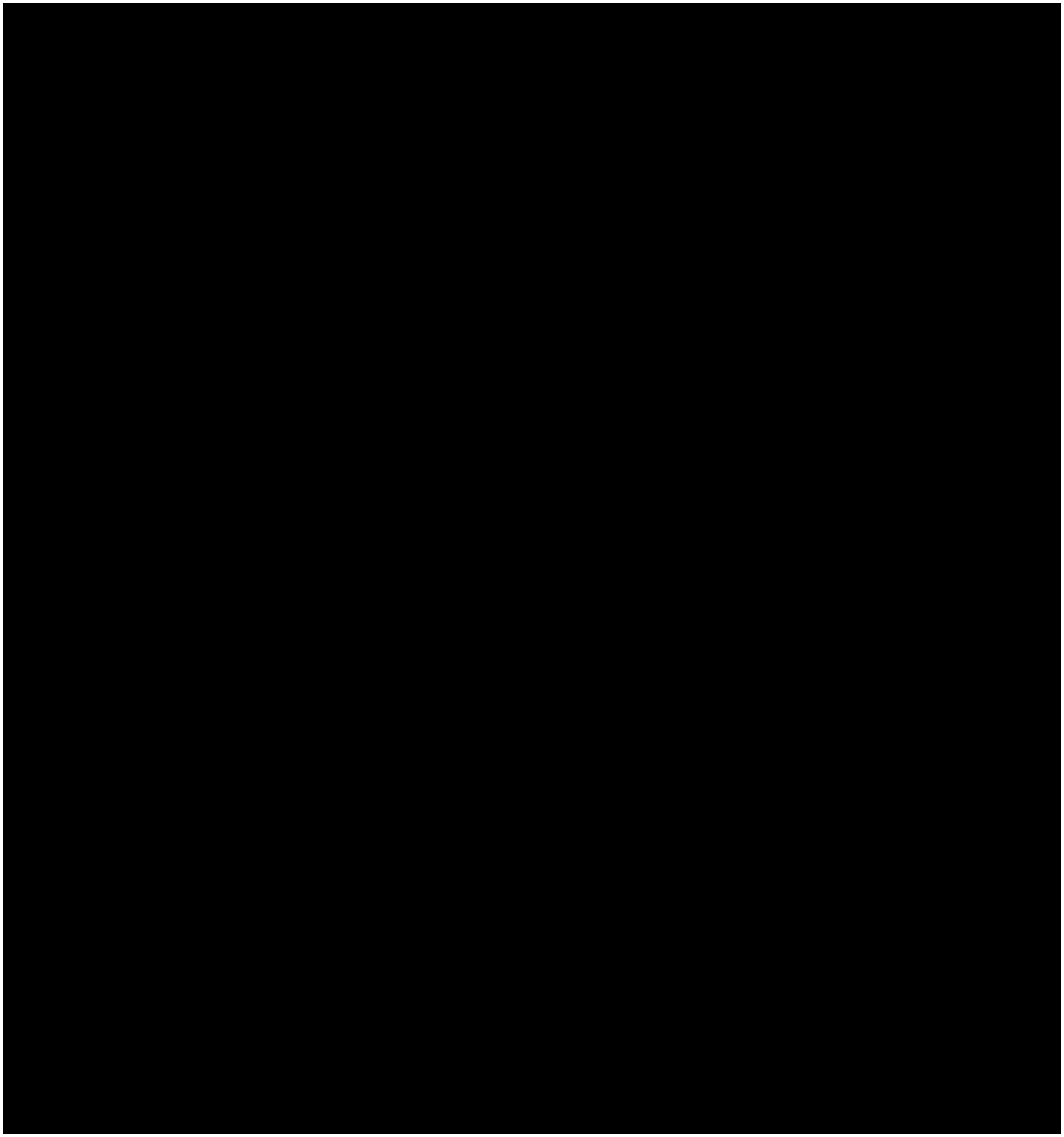
ASAS40

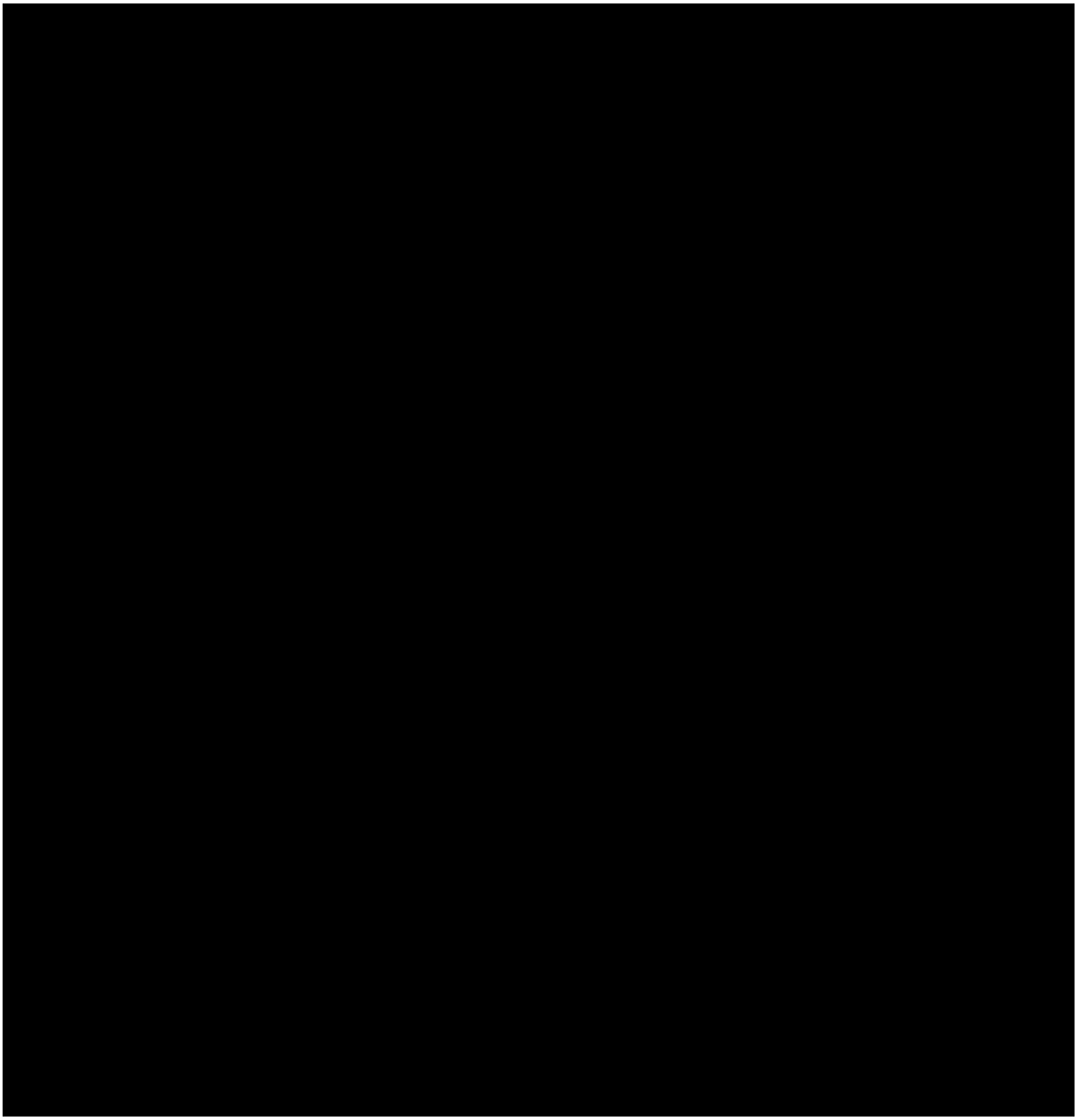
The ASAS 40 response is defined as an improvement of ≥ 40% and ≥ 2 units on a scale of 10 in at least three of the four main domains and no worsening at all in the remaining domain.

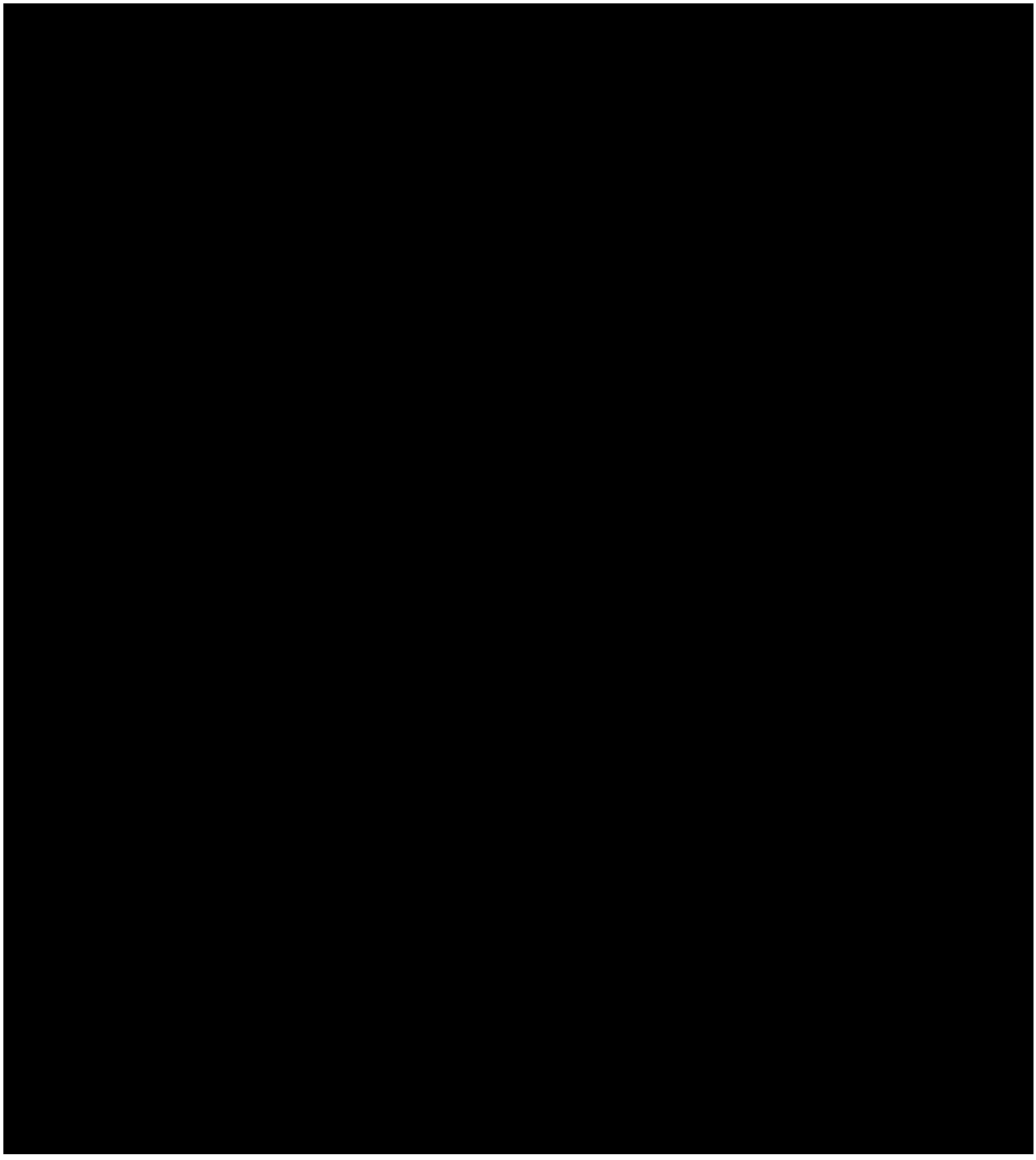
The percentage of subjects experiencing ASAS40 response, followed by the respective 95% CI will be presented by treatment sequence up to week 260 based on the observed data. The respective summaries will also be provided by TNF-α IR status.

Additional analysis will be based on the imputed responses only for the AIN457 150 mg group.

The percentage of subjects (and the 95% CI) experiencing ASAS40 response after up-titration will be presented in separate tables (observed data). Patients who had at least 1 dose of the up-titrated dose will be included.







16 Safety evaluation

Safety analyses will be done on the safety set.

Analysis of adverse events will be based on treatment emergent events, which are defined as events started after the first dose of study treatment in core study or events present prior to the first dose of study treatment in core study but increased in severity based on preferred term and within last dose + 84 days.

Other safety variables will be based on on-treatment events, which are defined as any events that happened after first dose of study treatment and within last dose + 84 days.

Summaries (other than by visit analysis) will be presented cumulatively from core and extension. For subjects who switched from placebo to secukinumab in the core study, their data prior to switch will not be reported. Safety on placebo will be based on the core study and will be reported in the in-text outputs and study listings.

Unless otherwise mentioned, by visit analysis will include the following visits: Baseline visit from core, Week 104E1 visit and all visits in extension. Summaries will be performed for all the events that happened within the last dose + 84 days.

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 if a subject received the wrong treatment during the entire study or if the subject up-titrated to a higher dose..

Subjects who switch treatment during the study (e.g. from placebo to active treatment, or escalated the dose) will be counted to both groups using the corresponding start and stop exposure date.

16.1 Adverse events

The crude incidence of treatment emergent adverse events on secukinumab (i.e. events started after the first dose of secukinumab in core study or events present prior to the first dose of secukinumab but increased in severity based on preferred term and within 84 days after last dose of secukinumab) will be summarized by primary system organ class and preferred term for the entire treatment period. CIs for the crude rate will be derived as described in Section 19.3.3.

In addition, exposure time-adjusted rates (incidence rate) including 95% CIs will be provided for selected terms for the entire treatment period (see Section 19.3.5) to adjust for differences in exposure.

Adverse events reported will be presented in descending frequency according to the incidence in total secukinumab group (combining all secukinumab treatment groups) starting from the most common event.

Summary statistics will be provided by primary system organ class and preferred term for the entire treatment period for all TEAEs, for serious TEAEs, for deaths, for TEAEs causing treatment discontinuation, for TEAEs possible related to study treatment, for TEAEs leading to temporary dose interruptions, for other serious or clinically significant treatment emergent adverse events or related discontinuations, for SPP risks and for adjudicated major adverse cardiovascular events (MACE). Additionally, summary statistics by 26 and 52 weeks intervals will be displayed reflecting the long term safety. For these tables the AEs will be counted only at the interval they were initially observed. If another AE with the same PT is starting again in a following time interval then it will be counted again at this interval.

Summaries (crude incidence only) will be presented for TEAEs by maximum severity as well. 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.

Adverse events separately by SMQ according to MedDRA using a narrow search will also be reported..

Exposure adjusted incidence rates for TEAEs by SMQ and preferred term, for selected lower lever risk terms based on TEAEs, serious adverse events, SPP risks and MACE, common and/or very common AE will be summarized by primary system organ class for the entire period.

The following AE terms are defined as lower lever risk terms:

- Dyspnea (PT)
- Seasonal allergy (PT)
- Colitis ulcerative (PT)
- Crohn's disease (PT)
- Inflammatory bowel disease (PT)
- Upper respiratory tract infections (HLT)
- Candida infections (HLT)
- B-cell lymphoma (PT)
- Bladder transitional cell carcinoma (PT)
- Breast cancer (PT)
- Lymphoma (PT)
- Malignant melanoma (PT)
- Dermatitis (PT)
- Eczema (PT)
- Rash(PT)
- Leukopenia (PT)
- Neutropenia (PT)
- White blood cell count decreased (PT)
- Dyspnea (PT)
- Seasonal allergy (PT)
- Diarrhea Hemorrhagic (PT)
- Squamous cell carcinoma (PT)
- Urticarial (PT)
- Uveitis (PT)
- Drug related hepatic disorders – severe events only (SMQ)(broad)
- Liver related investigations, signs and symptoms (SMQ) (broad)

The above list maybe modified based on the clinical team's advice.

As selection criterion for the common AE is the frequency of them of at least 2% in the initial treatment period (up to week 16) or IR of at least 5 during the entire treatment period as observed in the Any AIN457 group. The very common AE are defined in Core Data Sheet V2.1 (17-Mar-2017), Table 7.1. These include the following PTs: Nasopharyngitis, Upper respiratory tract infection, Rhinitis, Pharyngitis, Oral herpes, Rhinorrhoea, Diarrhea, Urticaria.

The incidence of AEs will be presented per 100 subject years of exposure.

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

If needed, follow-up period summaries will be done for all subjects in follow-up in this extension study (completers and early discontinuations).

AE listings will be limited to deaths, non-fatal SAEs, AE requiring treatment discontinuations and adjudicated MACE events.

Algorithms for date imputations in the AE listings are provided in PDS.

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

Listings will be provided for all adverse events, all non-fatal serious adverse events, deaths, adverse events leading to discontinuation from study treatment or temporary dose interruption, adverse events by SPP risks and adjudicated MACE events (myocardial infarctions, strokes, and cardiovascular deaths).

The safety analyses and which will be performed for treatment emergent AEs, labs, ECG and vital signs are described in Table 16-1 below.

Table 16-1 Overview of analyses on major safety endpoints

Analysis period	AEs & SAEs	AEs by severity	Study drug related AEs	AEs-SMQ	SPP Risk	Notables for (vitals/ ECG), lab criteria
Entire treatment period	• crude incidence • exposure time adjusted incidence*	• crude incidence	• crude incidence	• exposure time adjusted incidence*	• crude incidence • exposure time adjusted incidence*	• crude incidence

*Exposure-adjusted incidence rates will be done for the following:

- at the PSOC for AE and SAE
- at the PT level for common AEs, which is defined as at least 2% of the patients in the combined AIN457 groups during the initial treatment period or events that had an incidence rate of at least 5.0 cases per 100 subject-years in the combined AIN457 groups during the entire treatment period
- at Level 1 for Risks and SMQ analyses

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on <treatment emergent> adverse events which are not serious adverse events with an frequency greater than 5% and on <treatment emergent> serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

The tables will include data based on the safety population.

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.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective will be included.

16.2 Laboratory data

The summary of lab data will only include on treatment data, which are defined as those lab assessments after the first dose of secukinumab in core and on or before last dose + 84 days.

The summary of laboratory evaluations will be presented for hematology, chemistry and urinalisis. In addition to the individual laboratory parameters the ratios "total cholesterol / HDL" and "apolipoprotein B / apolipoprotein A1" will be derived and summarized.

For urinalysis frequency tables will be presented in this final lock.

Descriptive summary statistics for the change from baseline to each study visit in extension will be presented. These descriptive summaries will be presented by laboratory test and treatment dose. Baseline data from core study will also be included in these summaries. Change from baseline will only be summarized for subjects 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 (maximum decrease and maximum increase) from baseline, if appropriate for each study phase, will be analyzed.

In addition, shift tables will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. If appropriate, the shifts to the most extreme laboratory test value within the entire treatment period will be presented as well (including category "high and low"). These summaries will be presented by laboratory test and treatment dose.

Reported laboratory assessments with either a less than or greater than sign ("<" or ">") will be used for analysis after removal of the sign and conversion to standard unit. These laboratory data will be displayed in listings using the standard unit with the reported sign ("<" or ">")."

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in Table 16-2: 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 16-1 CTCAE grades for laboratory parameters to be analyzed

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	<LLN – 100 g/L	<100 – 80 g/L	<80 g/L	Life-threatening consequences; urgent intervention indicated
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

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
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 x ULN	>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	>10.34-12.92mmol/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 entire treatment period. Of note, baseline will be defined as last assessment prior to first dosing in initial treatment phase. Subjects 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 16-3 below:

Table 16-2 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

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 subjects with newly occurring or worsening liver enzyme and lipid parameters abnormalities, or for subjects with newly occurring or worsening after baseline CTCAE grades.

16.3 Vital signs

The summary of vital signs will only include on treatment data, which are defined as those vital sign measurements after the first dose of study treatment and on or before last dose + 84 days.

Analysis in vital sign measurement using descriptive summary statistics for the change from baseline for each post-baseline visit in extension will be performed. These descriptive summaries will be presented by vital sign and treatment dose. Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as: change from baseline = post-baseline value – baseline value

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 16-4 below.

Table 16-3 Criteria for notable vital sign abnormalities

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

16.4 Electrocardiogram (ECG)

The summary of ECG will only include on treatment data, which are defined as those ECG measurements after the first dose of study treatment and on or before last dose + 84 days.

The following quantitative variables will be summarized: ventricular rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTc). Both Bazett (QTcB) and Fridericia (QTcF) corrections will be presented for QTc.

QTc will generally be summarized by computing the number and percentage of subjects (including 95% CIs for pooled analyses, e.g. DMC or SCS) with:

- QTc > 500 msec
- QTc > 480 msec
- QTc > 450 msec
- QTc changes from baseline > 30 msec
- QTc changes from baseline > 60 msec
- PR > 250 msec

Summary statistics will be presented by visit and treatment dose in safety population.

Subjects with notable abnormal ECG parameters as described above, after baseline will be summarized.

Shift tables comparing baseline ECG interpretation (normal, abnormal, not available, total) with the worst on-study interpretation (normal, abnormal, not available, total), listing of all newly

occurring or worsening abnormalities, as well as a by-subject listing of all quantitative ECG parameters.

16.5 Immunogenicity

A listing of immunogenicity (anti-AIN457 antibodies) together with a listing with the impact of ADA development on the primary efficacy will be provided.

16.6 Compound specific safety evaluation

Safety topics of interest, such as risks defined in the Safety Profiling Plan, Risk Management Plan or topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet that is stored in CREDI at the path *Cabinets/CREDI Projects/A/AIN457A/Integrated Medical Safety*.

The crude incidence and exposure-adjusted incidence rates will be summarized. In addition, listings will be provided presenting which subjects experienced which risk.

Important note: For the evaluation of SPP risks primary and secondary system organ classes of the MedDRA dictionary (latest version) will be considered.

17 Interim analyses

Interim analyses are planned in order to support regulatory filing and for purpose of publication after subjects complete additional years of treatment in this extension study. Additional analyses may be performed to support health authority interactions, as necessary.

18 Determination of sample size

It is estimated that approximately 75% to 85% of subjects enrolled in the core study will complete the entire treatment period and be eligible for entry into the extension study, which is equivalent to about 279 to 316 subjects.

19 Appendix

19.1 Visit Windows

When visit windows are used (only for the core study), 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).

For lab/ECG/vital signs, follow-up (F/U) visit is excluded from analysis visit mapping window. Only assessments that come as F/U nominal visit will be directly assigned as analysis F/U visit. Other assessments that are beyond the last on-treatment visit window (Week 104) or after nominal F/U visit date won't be mapped to any analysis visit. F/U visit will not be included in the summary tables by visit.

During the extension study (after week 104E1) only nominal visits will be considered for the analysis.

Of note, subjects are allowed to have gaps in visits. All data collected will be displayed in listings at pre-specified analyses.

Table 19-1 Analysis visit windows (applied only for the core study)

Analysis Visit	Target Day	Analysis Visit Window	Group1	Group2	Group3	Group 4	Group 5	Group 6	Group 7	Group 8
Baseline	1	Up to Day 1*	Up to Day 1*	Up to Day 1*	Up to Day 1*	Up to Day 1*	Up to Day 1*	Up to Day 1*	Up to Day 1*	Up to Day 1*
Week 104E1	729	716-743	548-911	31-1093	632-813	660-813	548-813	716-771	688-771	548-813
Week 108E1	757	744-771								
Week 112E1	785	772-799								
Week 116	813	800-855						772-855	772-855	
Week 128	897	856-939			814-995	814-995	814-995	856-939	856-939	814-939
Week 140	981	940-1037						940-1037	940-1037	940-1037
Week 156	1093	1038-1135	912-1275		996-1177	996-1177	996-1177	1038-1135	1038-1135	1038-1135
Week 168	1177	1136-1219						1136-1219	1136-1219	1136-1219
Week 180	1261	1220-1303			1178-1359	1178-1359	1178-1359	1220-1303	1220-1303	1220-1303
Week 192	1345	1304-1401						1304-1401	1304-1401	1304-1401
Week 208	1457	1402-1499	1276-1639	1094-1835	1360-1541	1360-1541	1360-1541	1402-1499	1402-1499	1402-1499
Week 220	1541	1500-1583						1500-1583	1500-1583	1500-1583
Week 232	1625	1584-1667			1542-1723	1542-1723	1542-1723	1584-1667	1584-1667	1584-1667
Week 244	1709	1668-1765						1668-1765	1668-1765	1668-1765
Week 260	1821	1766-1835	1640-1835		1724-1835	1724-1835	1724-1835	1766-1835	1766-1835	1766-1835

Group 1: [redacted], Cardiovascular panel,
Group 2: X-Ray
Group 3: Lipids
Group 4: weight
Group 5: ECG,
Group 6: Physical exam, Vital signs
Group 7: Hematology, Blood chemistry, Urinalysis, Patient's global assessment of disease activity, Patient's assessment of spinal pain, [redacted], [redacted], Urine pregnancy test
Group 8: [redacted]
* The first administration of study treatment (first dose in core) is defined as Day 1.

The following rules are used to determine the window for an applicable visit post baseline: "Lower limit" = "upper limit of prior applicable visit" + 1. "Upper limit" = "target of current visit" + integer part of ("target of next applicable visit" – "target of current visit")/2. Lower limit of the first applicable visit is always 2.

The mapping described above applies to all core 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 19-2 Rules for flagging variables

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). Baseline assessments scheduled for and captured on Day 1 will be considered baseline measurements regardless of the time of assessment. If a patient did not receive any dose of study treatment then the randomization date will be used.
Post-baseline efficacy during the core study phase	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.
Post-baseline safety during the core study phase	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.
Post-baseline safety during the core study phase	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.

No visit windows were used in case of up-titrations. The before up-titration measurement is considered as the last visit measurement, performed on or before the date that patient took the up-titration dose. The up-titration data analysis will be based on week intervals; it is accounting for the time period between the actual date of exposure to the up-titrated dose and the last visit date of the subject:

- 4 – 8 weeks after up-titration
- 12 – 20 weeks after up-titration
- 24 – 32 weeks after up-titration
- 36 – 44 weeks after up-titration
- 48 – 60 weeks after up-titration

19.2 Statistical methodology and assumptions

19.2.1 Summary statistics for continuous data

Summary statistics (including N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum) will be provided for continuous data by visit and treatment group.

19.2.2 Analysis of covariance

Endpoints with continuous data type expected to be normally distributed (change from baseline) will be analyzed using a mixed-effects repeated measures model (MMRM). The explanatory variables will be weight, TNFα status, analysis visit, analysis visit by baseline score and baseline score. Since the MMRM will be applied only to the originally randomized AIN457 150 mg group the treatment factor will not be included in the model. An unstructured correlation matrix will be used thus allowing adjustment for correlations between time points within subjects.

SAS code for mixed model:

proc mixed data=<*aaa*>;

class TRT USUBJID AVISITN;

model CHG= WEIGHT TNFα AVISITN BASE BASE*AVISITN / s ddfm=kr;

lsmeans AVISITN / 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 BASE*AVISITN.

19.2.3 Summary statistics for binary and categorical data

Summary statistics for discrete variables will be presented in contingency tables and will include count and frequency in each category. If applicable, CIs will be derived as well based on the score method including continuity correction (Newcombe 1998):

With z as (1-alpha/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 then L = p and if U < p then U = p.

If appropriate, an exact 100*(1-α)% CI (Clopper-Pearson 1934) will be obtained by using the SAS procedure PROC FREQ with the EXACT BINOMIAL statement. However, the CI derived via the score method including continuity correction will be the default in safety analyses.

19.2.4 Multiple Imputation

A multiple imputation will be performed based on MAR by treatment group for baseline weight, baseline and post-baseline of each parameter for visits up to 156) using Markov Chain Monte Carlo (MCMC) method with EM algorithm.

Impute the missing values 100 times (NIMPUTE) with a seed=457<studycode> as shown below:

```
proc mi data=<xxx> out=imp minmaxiter=10000000 nimpute=100 seed=4572305;
        by trt;
        var weight_base tnfa var1_base var1_week1-var1_weekx;
        mcmc chain=multiple initial=em;
run;
```

If needed, repeat for each component necessary to calculate the final score, e.g. as follows:

```
proc mi data=imp out=imp2 minmaxiter=10000000 nimpute=100 seed=4572305;
        by trt _imputation_;
        var weight_base var2_base var2_week1-var2_weekxx;
        mcmc chain=multiple initial=em;
run;
```

All imputed variables are subject to post processing. If the imputed value is lower/greater than the absolute minimum/maximum of the parameter, then the imputed value will be set to the respective lowest/maximum possible value.

Example for Visual Analogue Scale (VAS), range=[0-100]

If the imputed value is negative then it will be set at 0

If the imputed value is greater than 100 then it will be set at 100.

For the imputation of ASAS20/40 and regarding the components of lateral lumber flexion and CRP the following should be noted:

- Lateral lumbar flexion: if the normal distribution is not strongly violated, no transformation will be employed.
- CRP will be impute at ln(CRP + 1). Then it should be transform back.

The responses now can then 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=<ASAS20>;
        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;
```

Of note, sometimes all responses may be imputed to 0 or 1 at a given combination of response variable, treatment group and visit. Such cases should be considered separately. The combined final response rate would be the same as the original response but the 95% CI will be undefined.

19.2.5 Exposure adjusted incidence rate and 100*(1-α)% CI

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 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 $T = \sum_{j=1}^{n} t_j$ and D is the number of subjects with at least one event. Conditionally on T, an exact 100*(1-α)% CI for a Poisson variable with parameter θT and observed value D can be obtained based on (Garwood, 1936), from which an exact 100*(1-α)% CI for D/T will be derived as follows (Sahai, 1993; Ulm, 1990):

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

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

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

The example below shows how this should be handled for cases where subjects switch treatment. In particular for summarizing 'Any AIN' as a group, one should take into consideration the sequence of treatments while calculating exposure time for subjects.

Table 19-3 Examples for calculating exposure time for incidence rates (IR)

1st treatment	1st exposure	2nd treatment	2nd exposure	Event days (in terms of study day)	Exposure for IR
Placebo	100 days	150 mg	200 days	50 (1st trt) 110 (10 days into 2nd trt)	Placebo: 50 days (event) 150 mg: 10 days (event) Any AIN: 10 days (event)

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