Clinical Development

Secukinumab (AIN457)

Clinical Trial Protocol [CAIN457F2306E1] / NCT01892436

A three-year extension study to evaluate the long term efficacy, safety and tolerability of secukinumab in patients with active psoriatic arthritis

RAP Module 3 Week 260 Detailed Statistical Methodology Amendment 1

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Document History – Changes compared to previous version of RAP module 3 week 260.

Amendment	Date	Change
Amendment 1	12 March 2018	Section 2. [redacted]
		Paragraph 14.1 Adverse Events The population required for the two tables on the Adverse events based on the legal requirements of ClinicalTrials.gov and EudraCT (<on-treatment/treatment emergent> adverse events which are not serious adverse events with an frequency greater than 5% and on <on-treatment/treatment emergent> serious adverse events and SAE suspected to be related to study treatment) has changed to safety population. "The tables will include data only from the extension part of the trial.", changed to "The tables will include data from the core and the extension part of the trial."
		Paragraph 12.5. The following text is added: "Shift tables will be provided comparing the subject's ACR evaluation at the pre up-titration visit relative to the observed data of the following week intervals after up-titration: (12-32 weeks), (36-56 weeks) and (60-80 weeks)."
		Paragraph 12.5. The following text is added: [redacted]

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List of tables

List of abbreviations

ACR	American College of Rheumatology
ADA	Anti-Drug Antibodies
AE	Adverse event
ALT	Alanine aminotransferase/Serum Glutamic Pyruvate Transaminase (SGPT)
ANA	Anti-nuclear antibodies
ANCOVA	Analysis of covariance
Anti-CCP	Anti-cyclic citrullinated peptide antibodies
AS	Ankylosing Spondylitis
AST (SGOT)	Aspartate Aminotransferase/Serum Glutamic Oxaloacetic Transaminase
ATC	Anatomical Therapeutic Classification
BMI	Body Mass Index
BSL	Baseline
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
CRP (hsCRP)	(high sensitivity) C-Reactive Protein
DAS	Disease Activity Score
DMARD	Disease Modifying Anti-rheumatic Drug
DMC	Data Monitoring Committee
DNA	Desoxyribonucleic acid
DS&E	Drug Safety & Epidemiology
dsDNA Ab	Anti-double stranded DNA antibodies
eCRF	Electronic Case Report/Record Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
EMA/EMEA	European Medicnices (Evaluation) Agency
EoS	End of Study
ESR	Erthrocyte Sedimentation Rate

[redacted] [redacted]

FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GTL	Global Trial Leader
HAQ-DI©	Health Assessment Questionnaire – Disability Index
hCG	Human Chorionic Gonadotropin
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
IA	Interim Analysis
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC/EC	Independent Ethics Committee
[redacted]	[redacted]
IFU	Instructions for Use
IL	Interleukin
IN	Investigator Notification
IR	Incidence Rate
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intra Uterine Device
IUS	Intra Uterine System
i.v.	intravenous
[redacted]	[redacted]
LDL	Low Density Lipoprotein
[redacted]	[redacted]
LLN	Lower limit of normal

LLOQ	Lower Limit of Quantification
MAR	Missing At Random
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
mmHG	Millimeter mercury
MTX	Methotrexate
NSAID	Non-Steroidal Anti-Inflammatory Drug
NovDTD	Novartis Drug/Therapy Dictionary
[redacted]	[redacted]
PDS	Programming and Dataset Specifications
PFS	Pre-filled Syringe
PK	Pharmacokinetic
PoC	Proof of Concept
PRO	Patient Reported Outcome
PsA	Psoriatic Arthritis
QoL	Quality of Life
RA	Rheumatoid Arthritis
RBC	Red blood cells
RDC	Remote Data Capture
RF	Rheumatoid Factor
SAE	serious adverse event
s.c.	Subcutaneous
[redacted]	[redacted]
SJC	Swollen joint count
SpA	Spondyloarthritides
SUSAR	Suspected Unexpected Serious Adverse Reaction
TJC	Tender joint count
TNF	Tumor Necrosis Factor
TNFα-IR	TNFα Inhibitor Incomplete/Inadequate Responders
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
VAS	Visual Analog Scale

WBC	White blood cells

1 Introduction

Data will be analyzed by Novartis according to the data analysis section 9 of the study protocol. That 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

No multiple imputation techniques and no MMRM estimation will be performed due to the presence of up-titrators.

[redacted]

3 Study objectives

3.1 Primary objectives

To evaluate the long-term efficacy of secukinumab with respect to ACR20, ACR50 and ACR70 response over time up to Week 260 in subjects with active PsA and who complete the phase III study CAIN457F2306.

3.2 Secondary objectives

1. To evaluate the long-term efficacy of secukinumab with respect to:
   a. Changes in HAQ-DI relative to baseline over time up to Week 260
   b. The proportion of subjects with improvements from baseline in HAQ-DI meeting or exceeding minimal clinically important difference (MCID) over time up to Week 260
   c. The changes in DAS28 (utilizing hsCRP) relative to baseline over time up to Week 260
   d. The proportion of subjects achieving low disease activity (DAS28 $\leq$ 3.2) and disease remission as defined by DAS28 (DAS28 < 2.6) over time up to Week 260
2. To evaluate the long term safety and tolerability of secukinumab 75 mg and 150 mg as assessed by vital signs, clinical laboratory variables, and adverse events monitoring over time up to Week 260.

4 Data presentation

Data analyses will be presented by treatment groups or treatment sequence as appropriate

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% confidence intervals 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). Baseline from core and Week 104 visit data will be presented appropriately. No formal hypotheses testing will be done. Hence, the p-values and confidence intervals 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 not be reported in post text tables.

All listings will be presented by treatment groups. Safety listings will also include the placebo data.

5 Subjects and treatments

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 and have at least one post baseline assessment of efficacy during the extension period. Subjects will be analyzed according to the treatment assigned to.

(In this document extension FAS is referred as to 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 subjects from the extension FAS set who received at least one dose of the up-titration dose.

[redacted]

Psoriasis subset: The psoriasis subset will include all FAS subject who have ≥ 3% of the body surface area (BSA) affected by psoriatic skin involvement at baseline.

Nail subset: The nail subset will include all FAS subject who have psoriasis currently in nails at baseline.

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

5.1 Treatment groups

The arms included in efficacy tables are based on the treatment sequence (picturing also the up-titration) for the periods up to the final lock at week 260. Two separate columns will display the assigned and actual treatment resulting in the following treatment sequences:

Efficacy:

- AIN457 10 mg/kg - 75 mg
- AIN457 10 mg/kg - 75 mg - 150 mg
- AIN457 10 mg/kg - 75 mg - 300 mg
- AIN457 10 mg/kg - 150 mg
- Placebo - AIN457 75 mg
- Placebo - AIN457 75 mg - 150 mg
- Placebo - AIN457 75 mg - 300 mg
- Placebo - AIN457 150 mg

After week 52 the combination of assigned treatment will also be shown.

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

The treatment sequence following up-titration for the combined groups will be:

- AIN457 75 mg & Placebo - AIN457 75 mg - 150 mg
- AIN457 75 mg & Placebo - AIN457 75 mg - 300 mg
- AIN457 150 mg & Placebo - AIN457 150 mg – 300 mg

Cases might up-titrate twice; for these cases the treatment prior to each up-titration will be displayed (that is not the assigned treatment for the 2nd observed up-titration). Therefore, at the graphical representation of up-titration the actual treatment dose prior to the switch will be displayed.

Regarding safety, the arms included in the entire treatment period are as follows.

- Any AIN457 75 mg
- Any AIN457 150 mg
- Any AIN457 300 mg
- Any AIN457 (if appropriate)

Placebo group will be included at the in-text tables and listings of the CSR.

In the safety listings the groups will be the following:

- AIN457 10 mg/kg - 75 mg
- AIN457 10 mg/kg - 150 mg
- Placebo AIN457 75 mg
- Placebo AIN457 150 mg
- Placebo not re-randomized.

6 Subgroup definitions

The primary endpoint and secondary endpoints will be evaluated for TNF-alpha inhibitor status and by concomitant MTX use (ACR20/50, [redacted]).

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

Baseline and post-baseline definitions

In general, a *baseline* value refers to the core study and is the last measurement made prior to administration of the first dose of study treatment in core. Baseline information will be presented appropriately in the "by visit" summaries in both safety and efficacy tables.

A post-baseline value refers to a measurement taken after the first dose of study treatment in core study.

Analysis visit windows

For visits that occur on or before week 104, *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 the Appendix (17.1 Visit Windows).

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 will be presented. The number and percentage of subjects in the FAS who completed the period up to week 260 and/or the follow up visit and who discontinued the study prematurely (including the reason for discontinuation) will be presented for each treatment group (including the up-titrated groups).

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 will be presented for FAS. Data already collected for core study will be presented for the extension analysis subjects as well.

The following common background and demographic variables will be analyzed according to the treatment sequence.

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 (<90 kg or ≥90 kg)
- Smoking status at baseline

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

CASPAR, TNF-α history (naive or inadequate responder), ACR components, number of prior biologic PsA therapies, MTX use (yes or no) and dose at baseline, time since first diagnosis of PsA in years, and psoriasis involvement (proportion of patients with psoriasis of hands and feet, psoriasis of the nail, and target lesion diameter, psoriasis >= 3% of BSA), DAS28 CRP and DAS28 ESR scores, HAQ-DI, [redacted] and systemic use of glucocorticoids.

Unless otherwise specified, summary statistics for continuous variables will be presented for each treatment group, for each placebo-AIN457 group, for the combination of AIN457 and

placebo switchers and finally for all subjects (total) in the FAS. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and all subjects (total) in the FAS.

9 Medical history

Any condition entered on the *Relevant medical history / current medical conditions* CRF will be coded using the MedDRA dictionary. Data collected for core study will be used for the extension as well. Data will be summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary. Summaries for cardiovascular medical history and psoriasis history will be provided as well. Disease history and baseline characteristics will be presented by treatment group.

Smoking history will be summarized by treatment sequence.

Disease history will be displayed by treatment sequence. Unless otherwise specified, analyses will be based on the extension FAS.

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 received. The duration of exposure to study treatment will also be summarized by treatment received. 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 secukinumab 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 received. Any medication given at least once between the start of the first dose in this extension trial and the date of the last study visit + 84 days 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 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 psoriatic arthritis 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.

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

ACR 20/50/70

ACR20 is a binary response variable defined for each subject. A subject will be considered a responder according to ACR20 criteria if he/she has at least (i.e., ≥):

• 20% improvement from baseline in tender 78-joint count

• 20% improvement from baseline in swollen 76-joint count

• 20% improvement from baseline in at least 3 of the following 5 measures:

- Patient's assessment of PsA pain (VAS 100 mm)
- Patient's global assessment of disease activity (VAS 100 mm)
- Physician's global assessment of disease activity (VAS 100 mm)
- Patient self-assessed disability (Health Assessment Questionnaire [HAQ-DI©] score)
- Acute phase reactant (C-reactive protein [hsCRP]) **or** Erythrocyte sedimentation rate (ESR).

In the definition above, the *baseline* value refers to the last measurement made prior to administration of the first dose of study treatment in core study.

The primary objective of this long term efficacy and safety study is to evaluate the proportion of subjects achieving ACR20, ACR50 and ACR70 by visit. Primarily, CRP will be used to calculate ACR response; ESR will only be used in the event CRP is missing.

ACR50 and ACR70 are defined in the same way as ACR20 by replacing the 20% with 50% and 70% improvement from baseline, respectively.

ACRn represents the percent improvement on the continuous scale and from ACRn one can directly calculate ACR20, ACR50, and ACR70 using the appropriate cutoffs. This variable is defined as:

ACRn = min (x_1, x_2, x_3), where

x_1 = % improvement from baseline in tender 78-joint count

x_2 = % improvement from baseline in swollen 76-joint count

and x_3 = 3rd largest value of x_4, x_5, x_6, x_7, x_8 where,

x_4 = % improvement from baseline in Patient's assessment of PsA pain (VAS 100 mm)

x_5 = % improvement from baseline in Patient's global assessment of disease activity (VAS 100 mm)

x_6 = % improvement from baseline in Physician's global assessment of disease activity (VAS 100 mm)

x_7 = % improvement from baseline in Patient self-assessed disability (Health Assessment Questionnaire [HAQ©] score)

x_8 = % improvement from baseline in Acute phase reactant (C-reactive protein [hsCRP]) **or** Erythrocyte sedimentation rate (ESR)

ACRn can be computed even if up to two values of x_4, x_5, x_6, x_7, x_8 are missing. ACRn, theoretically, cannot be computed, if one or both of x_1, x_2 is/are missing OR more than three values of x_4, x_5, x_6, x_7, x_8 are missing.

Health Assessment Questionnaire - Disability Index (HAQ-DI)

The Health Assessment Questionnaire (HAQ©) was developed by Stanford University and is one of the most widely used measures to assess the long-term influence of chronic disease on a subject's level of functional ability and activity restriction. The disability assessment component of the HAQ (Health Assessment Questionnaire – Disability Index), the HAQ-DI, assesses a subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in eight categories of functioning including dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The stem of each item asks over the past week "Are you able to …" perform a particular task. Each item is scored on a 4-point scale from 0 to 3, representing normal (normal, no difficulty [0]), some difficulty [1], much difficulty [2], and unable to do [3].

Scoring for the eight functional categories and overall disability index scoring will be performed as follows:

There are eight categories; first score within each category:

- Dressing and Grooming, includes items 1 and 2
- Arising, includes items 3 and 4
- Eating, includes items 5, 6 and 7
- Walking, includes items 8 and 9
- Hygiene, includes items 10, 11, and 12
- Reach, includes items 13 and 14
- Grip, includes items 15, 16 and 17
- Activities, includes items 18, 19, and 20

The score for each category will be the single response within the category with the highest score (greatest difficulty). For example, in the "Eating" category, there are two answers (one for each item). If "Cut your food with a knife or fork" is marked as "3" and "Lift a full cup or glass to your mouth" is marked as "0", then the score for the "Eating" category would be "3" (the response indicating the greatest difficulty within the category). If a component question is left blank or the response is too ambiguous to assign a score, then the score that that category will be determined by the remaining completed question(s). However, if **any** "aids or devices" and/or "help from another person" items at the bottom of each page are checked, the category to which they apply will be adjusted upward to "2". If the basic score is **already** "2" or "3", the score remains unchanged. "Aids or devices" and "help from another person" can **only** change a category's score to "2"; they do **not** change the score to a "1" or a "3".

The score for the disability index will be the mean of the eight category scores. If more than two of the categories, or 25%, are missing, scale will not be scored. Otherwise, divide the sum of the categories by the number of answered categories. The higher score indicates greater disability.

HAQ-DI response

The HAQ-DI response is defined by an improvement of at least 0.3 score points compared to baseline.

[redacted]

Joint/bone structural damage

The primary score for analyses will be van der Heijde modified Total Sharpe score (vdH-mTSS) (van der Heijde 1999), The erosion score and joint space narrowing score will be analyzed in similar fashion.

Erosions will be assessed each hand (20 locations per hand) and each foot (6 locations per foot). The maximum erosion score is 200 for all 40 hand locations, and 120 for all 12 feet locations. Thus, the total possible erosion score is 320.

Joint space narrowing (JSN) will be assessed in each hand (20 locations per hand) and foot (6 locations per foot). The maximum score is 160 for all 40 hand joints, and 48 for all 12 feet joints. Thus, the total possible JSN score is 208.

Pencil-in-cup: Osteolysis of the proximal phalanx and the base of the distal phalanx resulting in a pencil like proximal phalanx covered by cup like base of the distal phalanx. Pencil-in-cup will be scored as “P” where applicable.

Gross Osteolysis: Osteolysis of the phalanx resulting in a loss of the normal joint structure, usually accompanied by shortening of the length of the phalanx. Gross osteolysis will be scored as “G” where applicable.

If a joint or bone is not visible (e.g. poor film quality, missing imaging, severe misalignment, flexion deformity, dislocation) at the timepoint, the individual joint or bone will be coded as Not Visible (N).

If radiographs at the timepoint show a joint or bone with surgical fusion, replacement (prosthesis), or amputation, then the joint or bone will be scored Surgically Modified (S).

To obtain the total vdH-S score, scores for erosions and JSN in both the hands and feet will be added together. Any “P” or “G” will be considered the maximal score for the feature (erosions and JSN) per location in the calculation of the total vdH-S score. Any “N” or “S” will be considered null in the calculation of the total vdH-S score. The range of scores is 0 ~ 528.

The joints are divided into 10 segments according to Table 12-1. In each segment an adequacy threshold is defined. For each segment, when the change from baseline values are available for at least the threshold number of joints, the change from baseline will be calculated for the segment, with missing joints imputed by the within-segment mean change over individual joints. Otherwise (i.e. if less than threshold number of joints have available change from baseline values), the segment change from baseline will be missing. When ≥ 6 segments have

evaluable change from baseline values, the overall change from baseline value will be calculated, with missing segments imputed by the mean change over segments. Otherwise (i.e. if ≤ 5 segments have evaluable change from baseline values), the overall change from baseline value will be missing.

Table 12-1 Segmental distribution

Segment	Total number of joints	Adequacy threshold	Joints at one side
PIP erosions	8	5	PIP2, PIP3, PIP4, PIP5
DIP erosions	8	5	DIP2, DIP3, DIP4, DIP5
MCP + thumb erosions	12	7	MCP1, MCP2, MCP3, MCP4, MCP5, INTERPHALANGEAL JOINT OF THE HAND
Wrist erosions	12	7	FIRST METACARPAL BONE, DISTAL RADIUS, DISTAL ULNA, TRAPEZOID-TRAPEZIUM, NAVICULAR BONE, LUNATE BONE
Foot erosions	12	7	MTP1, MTP2, MTP3, MTP4, MTP5, INTERPHALANGEAL JOINT 1
PIP JSN	8	5	PIP2, PIP3, PIP4, PIP5
DIP JSN	8	5	DIP2, DIP3, DIP4, DIP5
MCP + thumb JSN	12	7	MCP1, MCP2, MCP3, MCP4, MCP5, INTERPHALANGEAL JOINT OF THE HAND
Wrist JSN	12	7	CMC3, CMC4, CMC5, RADIOCARPAL, SCAPHOID-TRAPEZIUM, CAPITATE-NAVICULAR-LUNATE
Foot JSN	12	7	MTP1, MTP2, MTP3, MTP4, MTP5, INTERPHALANGEAL JOINT 1

The readings of the x-rays and the scoring will be performed centrally. Two central independent radiograph readers, both blinded to treatment arm and radiograph sequence, will analyze the digitized images. In the case that adjudication is needed, a third consensus read will be performed. The statistical analysis will use the adjudicated score, if available, or the average score from the two readers otherwise.

In the situation that a consensus is made, but not all joints are scored, the missing consensus score at an individual joint, both at baseline and post baseline, will be imputed with the average of the two individual readers' scores at the joint for the respective time point, then the consensus change from baseline (at patient level) is calculated based upon all individual joints with imputation at joint level.

[redacted]

[redacted]

DAS28, low disease activity and remission

The Disease Activity Score (DAS) is a combined index to measure the disease activity in patients with RA. [redacted]

The DAS28 is a measure of disease activity based on Swollen and Tender Joint Counts, CRP or ESR, and the Patient Global Assessment. A DAS28 score > 5.1 implies active disease, ≤ 3.2 low disease activity, and < 2.6 remission.

The following 28 joints will be assessed for tenderness and swelling: metacarpophalangeal IV (10), thumb interphalangeal (2), hand proximal interphalangeal II-V (8), wrist (2), elbow(2), shoulders (2), and knees (2).

The following formulas can be used to calculate the DAS28 with CRP (mg/L) or ESR (mm/hour).

DAS28-CRP = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*ln(CRP+1) + 0.014*PGA + 0.96

DAS28-ESR = 0.56*sqrt(tender28) + 0.28*sqrt(swollen28) + 0.70*ln(ESR) + 0.014*PGA

TJC28: 28 Tender joint count; SJC28: 28 Swollen joint count; CRP: C-reactive protein; PGA: Patient Global Assessment

If any component measurement is missing, DAS28 will be missing.

DAS28-CRP will be primary for analysis; DAS-ESR will be secondary.

DAS28-CRP (or ESR) remission is defined as a DAS28-CRP (or ESR) index score less than 2.6. Low disease activity is defined as DAS28-CRP (or ESR) index less than or equal to 3.2.

ACR Components

Tender 78 joint count and swollen 76 joint count

The 78 joints assessed for tenderness include the 2 temporomandibular, 2 sternoclavicular, 2 acromioclavicular joints, 2 shoulders, 2 elbows, 2 wrists, 2 first carpometacarpal, 10 metacarpophalangeal, 10 proximal interphalangeal, 8 distal interphalangeal joints of the hands, the 2 hip, 2 knee, 2 talo-tibial, 2 mid-tarsal, 10 metatarsophalangeal, 10 proximal interphalangeal, and 8 distal interphalangeal joints of the feet. All of these except for the hips are assessed for swelling. Joint tenderness and swelling are to be graded present (1) or absent (0). Synovial fluid and/or soft tissue swelling but not bony overgrowth represents a positive result for swollen joint count. Dactylitis of a digit in the foot or hand counts as one tender and swollen joint.

If the number of joints for which data were available (e.g., T) is less than 78/76 for the tender/swollen joint assessment, the number of tender/swollen joints (e.g., t) will be scaled up proportionately (i.e., 78*t/T or 76*t/T for tender or swollen joint count).

Patient's assessment of PsA Pain

The patient's assessment of pain will be performed using 100 mm visual analog scale (VAS) ranging from "no pain" to "unbearable pain" after the question "*Please indicate with a vertical mark (|) through the horizontal line the most pain you had from your psoriatic arthritis today*".

Patient's global assessment of PsA disease activity

The patient's global assessment of disease activity will be performed using 100 mm VAS ranging from "very good" to "very poor", after the question "*Considering all the ways psoriatic arthritis affects you, please indicate with a vertical mark (|) through the horizontal line how well you are doing today*".

Physician's global assessment of PsA disease activity

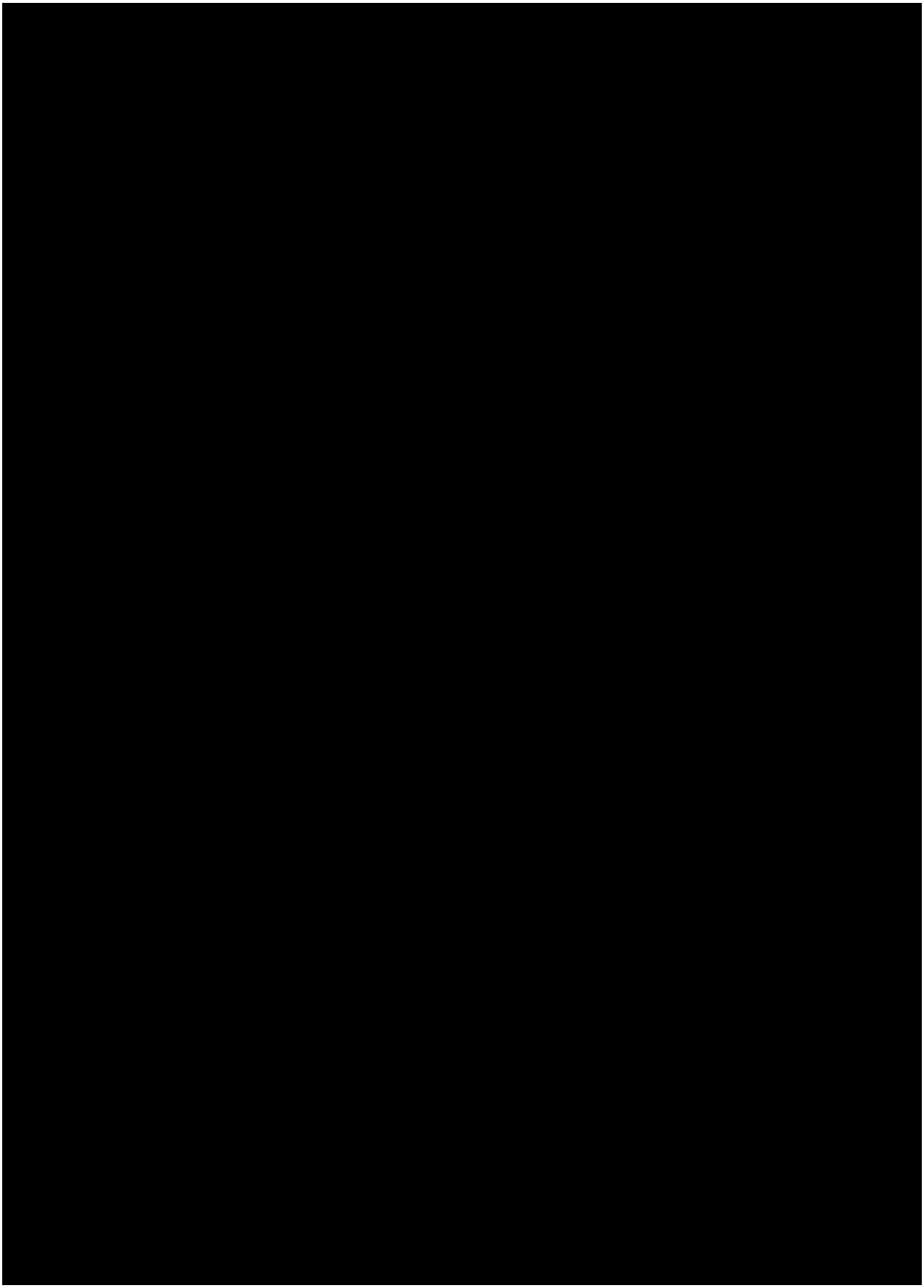
The physician's global assessment of disease activity will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question *"Considering all the ways the disease affects your patient, draw a line on the scale for how well his or her condition is today"*. To enhance objectivity, the physician must not be aware of the specific patient's global assessment of disease activity, when performing his own assessment on that patient.

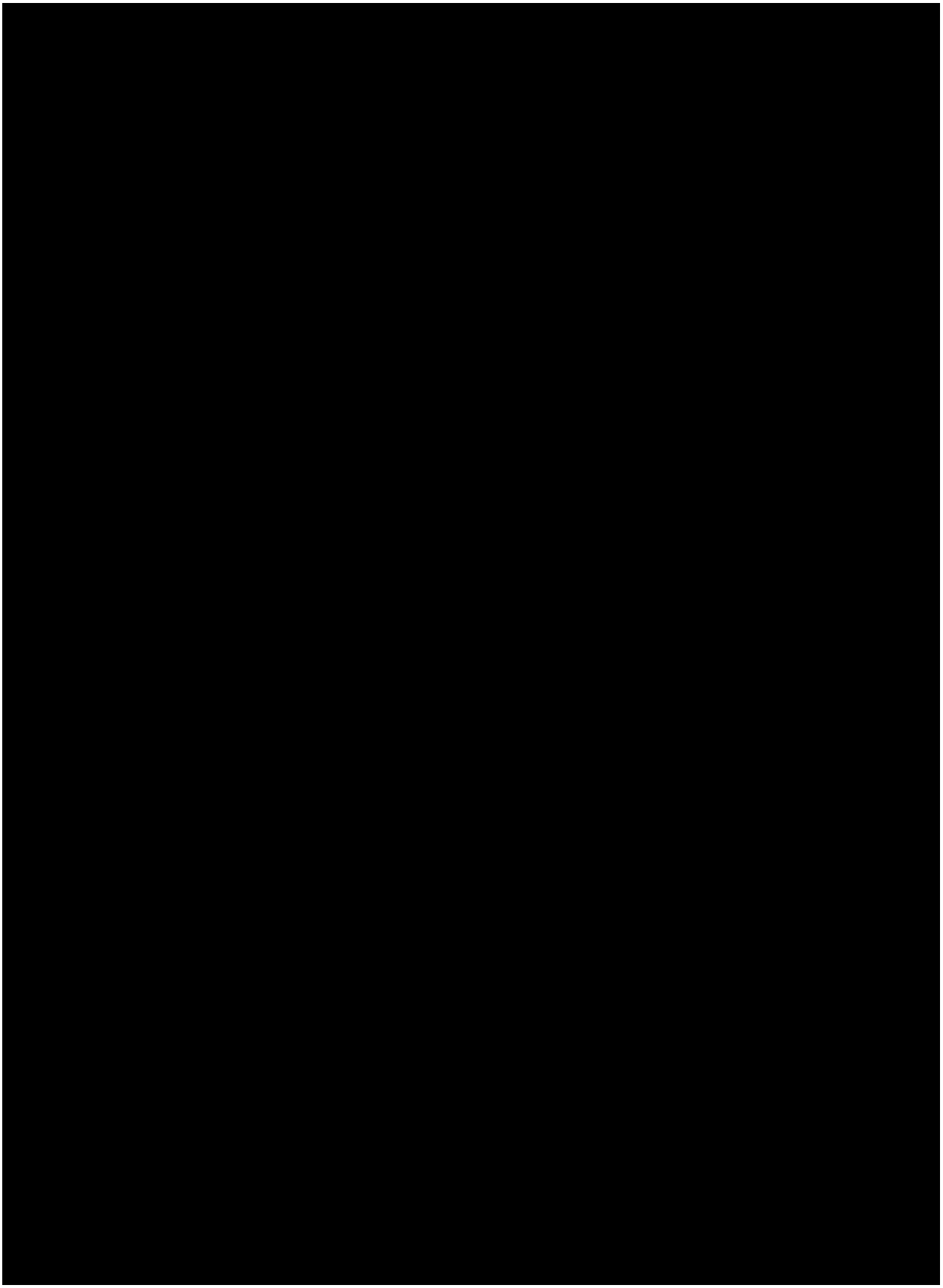
Erythrocyte sedimentation rate (ESR)

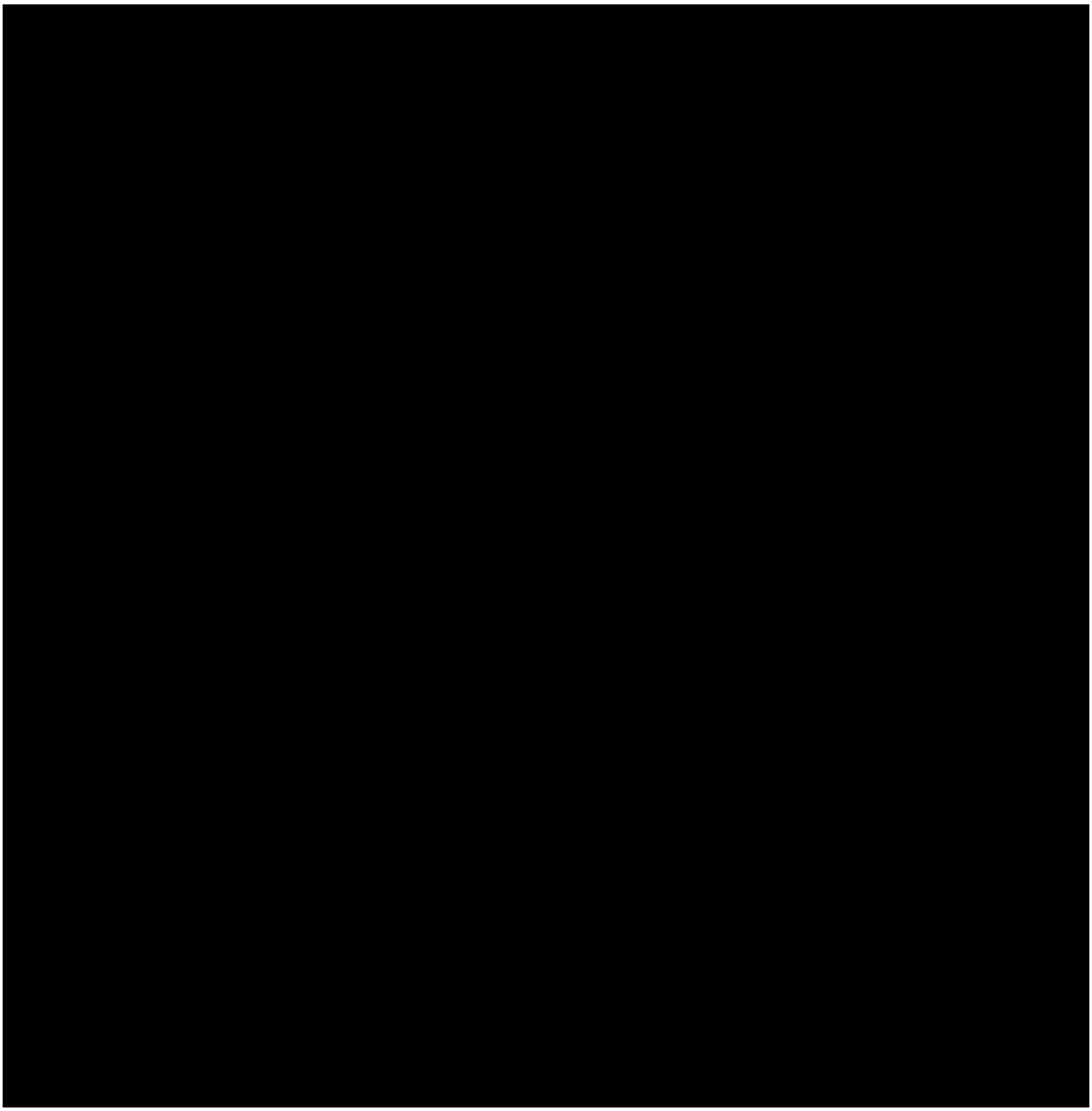
Blood for ESR, which is helpful in diagnosing inflammatory diseases and is used to monitor disease activity and response to therapy, will be obtained at scheduled visits.

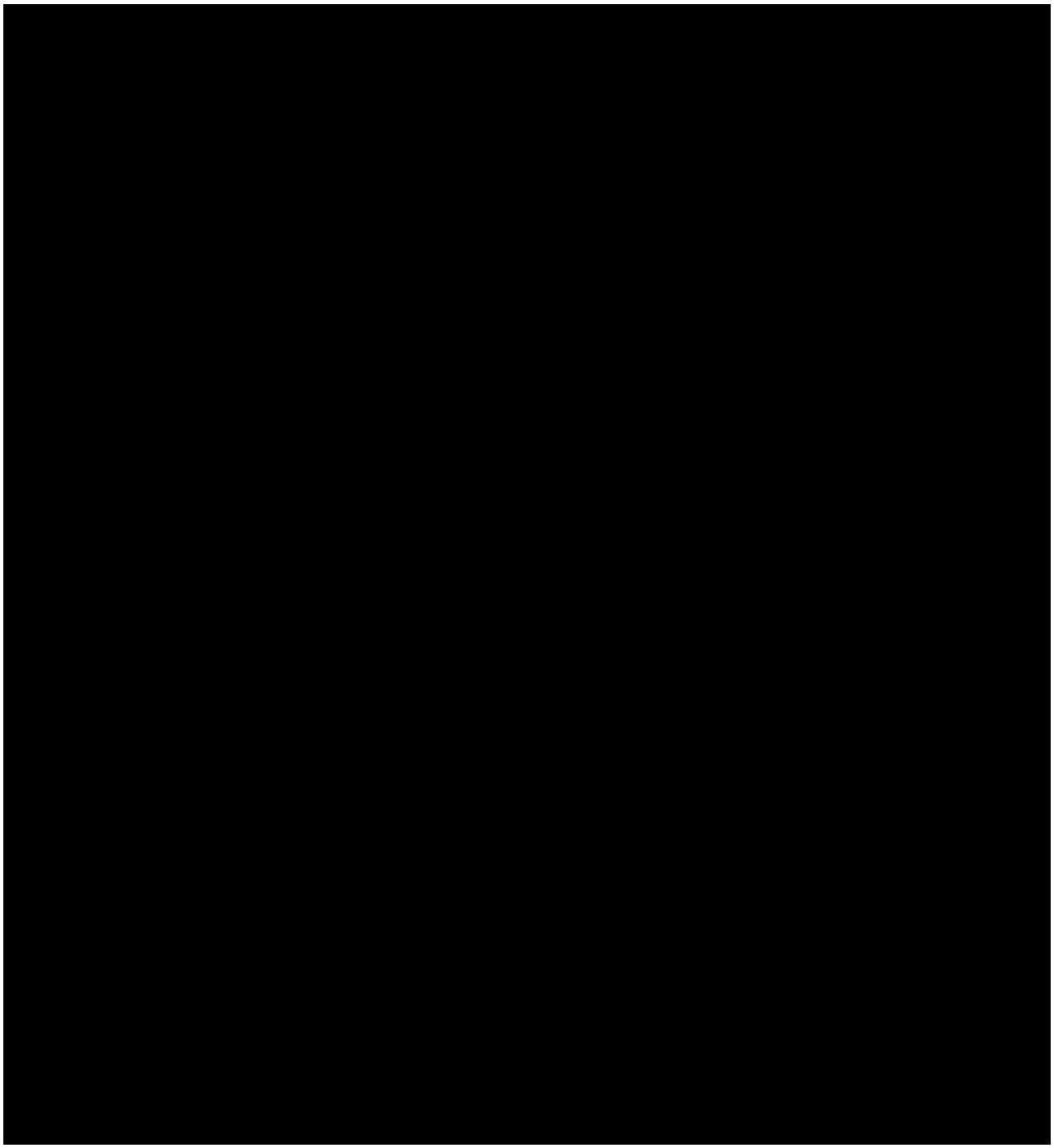
High-sensitivity C-reactive protein (hsCRP)

Blood for this assessment will be obtained in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment. Since the results of this test may unblind study personnel, results from the central lab will be provided for screening and baseline only. The hsCRP results from samples collected during the treatment period will be revealed following database lock only.









12.3 Handling of missing data

For primary analysis, data will be presented using all observed data at the given time point of analysis.

No multiple imputation or Mixed Models for Repeated Measures (MMRMS) will be considered since the influence of up-titrators in each group population violates the MAR assumption.

12.4 Analysis of Primary Variable(s)

The primary efficacy variable(s) is the clinical response to treatment according to ACR20, ACR50 and ACR 70 improvement in disease activity over time up to Week 260.

ACR response criteria denote the response (i.e., improvement) in signs & symptoms of the disease of a subject compared to baseline of the core study.

The analysis of the primary variables will be based on the FAS. Primarily, CRP will be used instead of ESR to calculate ACR response; ESR will only be used in the event CRP is missing.

Shift tables will be provided comparing the subject's ACR evaluation at the pre up-titration visit relative to the observed data of the following week intervals after up-titration: (12-32 weeks), (36-56 weeks) and (60-80 weeks). The ACR grouping presented in the table will be: ACR < 20, 20 $\leq$ACR < 50, 50 $\leq$ ACR < 70, ACR $\geq$ 70.

Graphical representation (line plots) of ACR20, ACR50 and ACR70 response over time and Sankey-style bar chart for the ACR response within the subjects that up-titrated from 150 mg to 300 mg (provided that up-titration has been occurred for more than 8 weeks) will be drawn from the observed data.

Additionally, observed data tables will summarize the ACR20, ACR50 and ACR70 response following up-titration when assessed. Results will be illustrated in line plots.

Also individual subject listings of the ACR components as well as for the ACR20/50/70 response will be given.

Statistical model, hypothesis, and method of analysis

No formal hypotheses are planned for this study. The proportion of subjects meeting the ACR criteria (ACR20, ACR50, and ACR70) will be descriptively summarized for each treatment by absolute and relative frequencies followed by 95% confidence intervals for the proportion of patients responding to treatment according to the ACR criteria from Week 1 onwards based on the pooled data from core and extension study. Results regarding ACR20/50/70, will be presented overall in the FAS population as well as in subgroups by TNFα status (naive or IR) and by concomitant use of MTX as appropriately.

Placebo group (core study) in efficacy analysis will not be considered.

Supportive analyses

Sensitivity analyses using multiple imputations for missing assessments for ACR 20, ACR 50 and ACR 70 will not be performed.

12.5 Analysis of secondary and exploratory variables

Secondary and exploratory variables for the final analysis of the extension study include:

- The change from baseline in HAQ-DI
- The proportion of subjects with improvements from baseline in HAQ-DI ≥ minimal clinically important difference (MCID=0.3)
- The change from baseline in DAS28-CRP
- The proportion of subjects achieving low disease activity (DAS28 ≤ 3.2) and disease remission as defined by DAS28 (DAS28 < 2.6)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

All the above efficacy variables will be analyzed on the FAS (unless otherwise specified) for all applicable analysis visits based on the observed data.

For binary variables, the proportion of responders along with the 95% CI will be presented by treatment groups over analysis visits.

For continuous variables, the change from baseline (of core) when available, will be summarized.

[redacted]

Figures will be provided for the following parameters:

- [redacted]
- DAS28-CRP and SF-36 PCS change from baseline.
- HAQ-DI score (change from baseline) overall and following the up-titration
- HAQ-DI response overall and following the up-titration
- HAQ-DI response by TNF-α inhibitor status.
- Remission response and low disease activity response according to DAS28-CRP
- [redacted].
- [redacted]

Individual listings will be considered for all efficacy variables of the study.

Joint/bone structural damage at Week 156, 208

The changes in joint/bone structural damage (total sharp score, and its components, erosion score and joint spacing narrowing score) will be summarized by the same treatment groups as follows using evaluable data of each x-ray reading session:

- Baseline to:
  - Week 24
  - Week 52
  - Week 104
  - Week 156
  - Week 208
- Week 24 to:
  - Week 52
  - Week 104
  - Week 156

    - Week 208
- Week 52 to:
    - Week 104
    - Week 156
    - Week 208
- Week 104 to:
    - Week 156
    - Week 208

The above analyses will be done on both FAS and X-ray completers where X-ray completers are those subjects that had X-ray measures at baseline, Week 16/24, Week 52, Week 104, Week 156 and Week 208. Subgroup analyses by TNF-alpha inhibitor status will be provided.

Analyses will be performed for each reading campaign, as appropriate depending on the available data.

For the purpose of the campaign 3 the readings of baseline, week 156 and week 208 will be used for the analysis. Any data on week 260 will be shown only in listings.

Individual listings will be provided for Joint structural damage components.

[redacted]

13 Pharmacokinetic evaluations (change / add PD, PK/PD, Biomarkers, as needed)

13.1 Pharmacokinetics

All completed subjects with quantifiable pharmacokinetic (PK) measurements of secukinumab will be included in the pharmacokinetic data analysis. Serum concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification as well as missing data will be labeled as such in the concentration data listings. PK concentrations will be summarized by visit and treatment group. In addition to mean, standard deviation (SD), coefficient of variation (CV), median and quartiles, the geometric mean and geometric coefficient of variation (CV) and n(log) will be presented. The formula for deriving the geometric mean and CV (%) is as following:

- CV (%) = (SD/mean)*100,
- geometric mean=exp((sum of log transformed data) / number of non-missing data points after log transformation),
- geometric CV = sqrt(exp(variance of log-transformed data)-1)*100.

In addition, sample number, concentration, sample date, sample time at pre-dose and minutes pre-dose will be listed by treatment sequence.

Values below lower limit of quantification/below detection limit will be imputed by 0.

Pharmacokinetic data of the study treatment will be analyzed with a population-pharmacokinetic mixed effects model. The analysis will be based on a pooled data set, including pharmacokinetic samples from previous studies. The modeling approach will be further detailed in a modeling plan. Results will be reported separately.

14 Safety evaluation

Safety analyses will be done on the safety set.

Summaries will be presented cumulatively from core and extension. For subjects who switched from placebo to secukinumab in core, their data prior to switch will only be reported in in-text tables and listings.

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 core and extension 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 had dose escalation) will be counted to both groups using the appropriate start and stop exposure date.

14.1 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. Confidence intervals for the crude rate will be derived as described in Section 17.2.3.1 In addition, exposure time-adjusted rates (incidence rate) including 95% confidence intervals will be provided for selected terms for the entire treatment period, (see Section 17.2.4.1) to adjust for differences in exposure.

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

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 possibly related TEAEs, for deaths, for TEAEs causing treatment discontinuation, other serious or clinically significant treatment emergent adverse events or related discontinuations, for TEAEs leading to temporary dose interruptions, for SPP risks and for adjudicated major adverse cardiovascular events (MACE). Separate summaries for adverse events suspected to be related to study drug, will also not be displayed in the current analysis.

TEAEs will also be summarized by primary system organ class and preferred term for the entire treatment period in time segments of 52 and 26 weeks.

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.

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.

Exposure adjusted incidence rates for TEAEs, selected lower lever risk terms based on TEAEs, serious adverse events, adverse events leading to discontinuation, common AEs (frequency >2% in the Any AIN457 group during the first 24 weeks of treatment or IR> 5/100 subject years during the entire treatment period), SPP risks and MACE will be summarized by primary system organ class and/or by preferred term for the entire period.

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

Exposure adjusted incidence rates for TEAEs will also be provided for specific common or very common TEAEs (very common TEAEs are described in the Core Data Sheet).

Adverse events will be reported separately by SMQ according to MedDRA. The MedDRA version used for reporting will be described in a footnote.

Algorithms for date imputations will be provided in the PDS.

The safety analyses that will be performed for treatment emergent AEs, labs, ECG and vital signs for each analysis period is described in table below.

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).

For SAEs that occurred during screening a listing will be prepared for all subjects screened including screening failures.

No graphical displays of the crude incidence rates and exposure-adjusted rates will be presented for any AEs and serious AEs by system organ class in the current interim analysis.

An overview of the safety analyses and which will be performed for each analysis period is described in Table 14-1.

Table 14-1 Overview of analyses on some safety endpoints

Analysis period	AEs & SAEs	AEs by severity	Study drug related AEs	AEs-SMQ	Risk	Notables for (vitals/ ECG), lab criteria
Entire Treatment	•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 <on-treatment/treatment emergent> adverse events which are not serious adverse events with an frequency greater than 5% and on <on-treatment/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 from the core and the extension part of the trial.

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.

14.2 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 three groups of laboratory tests (hematology, chemistry and urinalysis). In addition to the individual laboratory parameters the ratios “total cholesterol / HDL” and “apolipoprotein B / apolipoprotein A1” will be derived and summarized.

For urinalysis, frequency tables across visits will be presented.

Descriptive summary statistics for the absolute value at study visits as well as the change from baseline to extension study visits will be presented in tabular fashion. These descriptive summaries will be presented by laboratory test 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 maximum change (maximum decrease and maximum increase) from baseline for each lab parameter, will also be analyzed. Shift tables will be provided comparing the subject’s baseline laboratory evaluation relative to the visit’s observed data. 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 a treatment phase (either initial or entire) 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 14-2: 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.

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

Table 14-2 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
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 - 12.92 mmol/L	>12.92 mmol/L
Hypertriglyceridemia	1.71 - 3.42 mmol/L	>3.42 - 5.7mmol/L	>5.7 - 11.4 mmol/L	>11.4 mmol/L

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

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 14-3:

Table 14-3 Liver-related events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN, >20xULN
AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
ALT or AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
TBL	>1.5xULN, >2xULN, >3xULN,
ALP	>2xULN, >3xULN. >5xULN
ALT or AST & TBL	ALT or AST>3xULN & TBL >2xULN; ALT or AST >5xULN & TBL >2xULN; ALT or AST >8xULN & TBL >2xULN; ALT or AST >10xULN & TBL >2xULN
ALP & TBL	ALP >3xULN & TBL >2xULN ALP >5xULN & TBL >2xULN
ALT or AST & TBL & ALP	ALT or AST>3xULN & TBL >2xULN & ALP <2xULN **(Hy's Law**) Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of *pure hepatocellular injury*. This does not mean that cases of ALT or AST >3xULN & TBL >2xULN & ALP ≥2xULN may not result in severe DILI.
Notes:1) In studies which enroll subjects with pre-existing liver disease, baseline LFT may be increased above ULN; in such a case it is meaningful to add the condition "and worse than baseline" to the abnormality criteria	

For a combined criterion to be fulfilled, all conditions have to be fulfilled on the same visit. The criteria are not mutually exclusive, e.g. a subject with ALT = 6.42xULN is counted for ALT >3xULN and ALT>5x ULN.

Individual subject laboratory data listings will be provided for all subjects as well as for subjects with newly occurring or worsening CTCAE grades, or with newly occurring or worsening after baseline abnormalities in lipid parameters, or with newly occurring or worsening after baseline abnormalities in liver enzymes.

No box plots over time or other graphs will be presented for any of the laboratory parameters.

14.3 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 only be presented for subjects with both a baseline (of core study) and post baseline values. 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

Analysis in vital sign measurements using descriptive summary statistics for the change from baseline until each post-baseline visit will be performed.

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 13-4 below.

Table 14-4 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

Individual subject listing of vital signs and a listing for the newly occurring notably abnormalities will be provided.

14.4 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 only be summarized by computing the number and percentage of subjects (including 95% confidence intervals 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

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

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

Shift tables comparing baseline ECG interpretation (normal, abnormal, not available, total) with the worst on-study interpretation (normal, abnormal, not available, total) will be provided.

14.5 Immunogenicity

A listing of immunogenicity (anti-AIN457 antibodies) and a table with an overview of patients with anti-drug antibodies for patients with baseline or treatment emergent ADA will be provided.

14.6 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 for potential compound and class-related risks and routine risks 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 will be considered.

15 Interim analyses

Interim analyses are planned in order to support regulatory filing and for purposes of publication after subjects complete year 1 (Treatment period 3), and year 2 (Treatment period 4) of treatment in this extension study. Additional analyses may be performed to support health authority interactions, as necessary.

16 Sample size calculation

It is estimated that 80~90% of subjects originally randomized to secukinumab will complete the entire treatment period and be eligible for entry into the extension (320~360 subjects). Likewise, 70~80% of the subjects originally randomized to placebo (140~160 subjects) will be eligible. In total, it is estimated that 460~520 subjects will be eligible for enrollment in this extension study.

17 Appendix

17.1 Visit Windows

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 112* visit of a subject is delayed and occurs on Day 810 instead of on Day 785, say, it will be re-aligned to visit window *Week 116*. 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 or optional site visits). Statistical approaches to handle multiple assessments in a given visit window are specified below.

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 (W264) 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.

For visits that occur after week 104 only the recorded nominal visit should be used.

Of note, subjects are allowed to have gaps in visits. Optional site visits will not be presented in summaries but will be used for mapping to planned visits. All data collected will be displayed in listings.

Table 17-1 Analysis visit windows

Analysis Visit	Target Day	Analysis Visit Window	Group 1	Group 2	Group 3	Group 4	Group5	Group6	Group7	Group8	Group9	Group10	Group11	Group12	Group13	Group14	Group15
Baseline	1	Up to 1*	Up to 1*	Up to 1*	Up to 7	Up to 1*	Up to 1*	Up to 1*	Up to 1*	Up to 1*	Up to 1*	Up to 1*	Up to 30	Up to 1*	Up to 1*	Up to 1*	Up to 1*
Week 1	8	2-11	2-11	2-11					2-11								2-11
Week 2	15	12-22	12-22	12-22				2-22	12-22								12-22
Week 4	29	23-43	23-43	23-43			2-71	23-43	23-43	2-43						2-57	23-43
Week 8	57	44-71	44-71	44-71				44-71	44-71	44-71	2-85						44-71
Week 12	85	72-99	72-99	72-99	8-127			72-99	72-99	72-99						58-99	72-99
Week 16	113	100-127	100-127	100-127		2-141	72-141	100-141	100-141	100-141	86-141	2-239	31-141			100-141	100-127
Week 20	141	128-155	128-155	128-155													128-155
Week 24	169	156-183	156-183	156-183	128-449	142-267	142-267	142-197	142-197	142-267	142-267		142-267	2-267	2-267	142-197	156-183
Week 28	197	184-211	184-211	184-211													184-211
Week 32	225	212-239	212-239	212-253				198-253	198-253							198-253	212-239
Week 36	253	240-267	240-267														240-267
Week 40	281	268-295	268-295	254-323				254-323	254-323							254-323	268-295
Week 44	309	296-323	296-323														296-323
Week 48	337	324-351	324-351														324-351
Week 52	365	352-379	352-393	324-393		268-547	268-547	324-393	324-393	268-547	268-449	240-547	268-547	268-547	268-477	324-393	352-393
Week 56	393	380-407															

Analysis Visit	Target Day	Analysis Visit Window	Group 1	Group 2	Group 3	Group 4	Group5	Group6	Group7	Group8	Group9	Group10	Group11	Group12	Group13	Group14	Group15
Week 60	421	408-435	394-449	394-449				394-449	394-449							394-449	394-449
Week 64	449	436-463															
Week 68	477	464-491	450-505	450-505				450-505	450-505							450-505	450-505
Week 72	505	492-519															
Week 76	533	520-547	506-561	506-561				506-561	506-561		450-631					506-561	506-561
Week 80	561	548-575															
Week 84	589	576-603	562-617	562-617				562-617	562-617						478-659	562-617	562-617
Week 88	617	604-631															
Week 92	645	632-659	618-687	618-687				618-687	618-687							618-687	618-673
Week 96	673	660-687															
Week 100	701	688-715															674-715
Week 104	729	716-743	688-743	688-743	450-743	548-743	548-743	688-743	688-743	548-743	632-743	548-743	548-743	548-743	660-743	688-743	716-743

Group1: ACR components, HAQ-DI, Tender and Swollen Joints
Group2: Hematology, blood chemistry, urinalysis, skin test
Group4: WPAI-GH, cardiovascular panel
Group5: PK
Group6: [redacted]
Group7: [redacted]
Group8: [redacted]
Group9: Lipids
Group10: ECG
Group11: X-ray

Analysis Visit	Target Day	Analysis Visit Window	Group 1	Group 2	Group 3	Group 4	Group5	Group6	Group7	Group8	Group9	Group10	Group11	Group12	Group13	Group14	Group15
Group12: Immunology, [redacted]																	
Group13: Weight																	
Group14: Pregnancy test, hormones																	
Group15: Vital signs																	
* The first administration of randomized study treatment (first dose) is defined as 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 day of current visit" + integer part of ("target day of next applicable visit" – "target day of current visit")/2. Lower limit of the first applicable visit is always Day 2.

The mapping described above applies to all visits including optional site visits (not just scheduled visits). Optional site 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 17-2 Rules for flagging variables

Timing of measurement	Type of data	Rule
Baseline of core	All data	The last measurement made prior to administration of the first dose of study treatment in core– note this may include measurements taken on the day of randomization (e.g. lab). If a patient did not receive any dose of study treatment then the randomization date will be used.
Post-baseline efficacy	All data	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	Summary visit information (e.g. lab, ECG, etc.)	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	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 – 32 weeks after up-titration
- 36 – 56 weeks after up-titration
- 60 – 80 weeks after up-titration
- 84 – 104 weeks after up-titration

17.2 Interim Locks dates

Annual locks for analysis purposes were performed.

This the final lock of the study at week 260. It includes all subjects who have completed week 260 assessment and/or the follow up treatment visit.

17.3 Statistical methodology and assumptions

17.3.1 Analysis of continuous data

17.3.1.1 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.

17.3.2 Analysis of binary (and categorical) data

17.3.2.1 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, confidence intervals 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

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

SAS code for risk difference:

Proc freq data=acr order=formatted;

Tables response*trt/ riskdiff;

Run;

(Note the response value should be sorted with ‘1’ ahead of ‘0’.)

17.3.3 Crude incidence and related risk estimates

17.3.3.1 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:

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

and the upper limit is

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

Note: if L > (100 x p) then L = (100 x p) and if U < (100 x p) then U = (100 x p).

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

17.3.4 Exposure adjusted incidence rate and related risk estimates

17.3.4.1 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 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)% confidence interval 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)% confidence interval for D/T will be derived as follows (Sahai, 1993; Ulm, 1990):

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

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

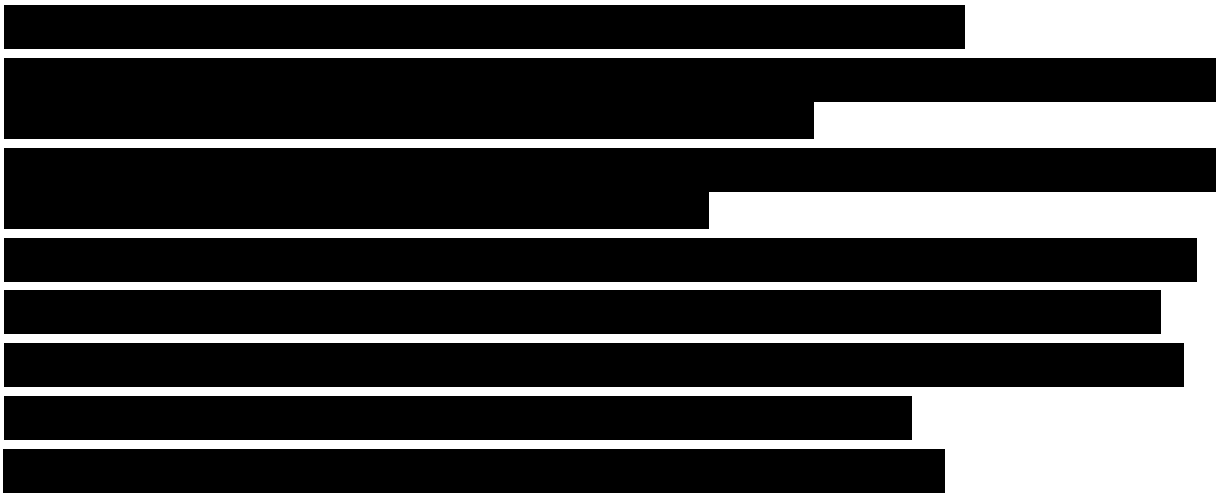
where $c_{\alpha,k}$ is the αth quantile of the Chi-square distribution with k degrees of freedom.

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 17-3 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)

18 References



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