NOVARTIS

Clinical Development

CAIN457/Secukinumab/Cosentyx®

CAIN457F2367 / NCT04711902

A phase III randomized, double-blind, placebo controlled, multicenter, bridging study of subcutaneous secukinumab, to demonstrate efficacy after sixteen weeks of treatment and to assess safety, tolerability and long-term efficacy follow-up to one year in Chinese participants with active psoriatic arthritis

Statistical Analysis Plan (SAP) for Final Analysis

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
6-Apr-2023	Prior to DBL	Amendment 1	Removed “AIN457 150 mg” group in the entire period	2.1.1.1 Treatment groups
6-Apr-2023	Prior to DBL	Amendment 1	Added a paragraph for disclosure purpose	2.7.1 Adverse events (AEs)
6-Apr-2023	Prior to DBL	Amendment 1	Added a sentence for potential additional analysis [redacted] as appropriate	[redacted]

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
ALB	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear antibody
Anti-CCP	Anti-cyclic citrullinated peptide
anti-dsDNA	anti-double stranded DNA antibodies
AS	Ankylosing Spondylitis
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
β-hCG	Beta human chorionic gonadotropin
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
BSL	Baseline
BUN	Blood Urea Nitrogen
°C	degree Celsius
CASPAR	Classification of Psoriatic Arthritis
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CFDA	China Food and Drug Administration
CFR	Code of Federal Regulation
CI	Confidence Interval
ClinRO	Clinician Reported Outcomes
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
COA	Clinical Outcome Assessment
COVID-19	Coronavirus disease 2019
COX-1	Cyclooxygenase 1
COX-2	Cyclooxygenase 2
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
csDMARDs	Conventional Synthetic Disease-Modifying Antirheumatic Drugs
CSR	Clinical Study Report
CTLA4 Ig	Cytotoxic T lymphocyte associated antigen-4 immunoglobulin fusion proteins
DAS	Disease Activity Score
DAS28-CRP	Disease Activity Score for 28 joints - C reactive protein
DLT	Dose Limiting Toxicity
DMARDs	Disease modifying antirheumatic drug(s)
DMS	Document Management System
DNA	Deoxyribonucleic Acid
EC	Ethics Committee

ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of study
eSAE	Electronic Serious Adverse Event
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
°F	degree Fahrenheit
[redacted]	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GCS	Gamma-glutamyl transferase
h	Hour
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HRQoL	Health-Related Quality of Life
hs-CRP	high-sensitivity C-reactive protein
IA	Interim Analyses
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions for Use
[redacted]	[redacted]
IL-17	Interleukin-17
i.v.	Intravenous(ly)
IVR	Interactive Voice Response
IWR	Interactive Web Response
[redacted]	[redacted]
LDL	Low Density Lipoprotein
[redacted]	[redacted]
LLN	Lower Limit Normal
LLOQ	Lower Limit of Quantification
MAR	Missing at Random
MCR	Major Clinical Response
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Drug Regulatory Affairs

MMRM	Mixed-effects model repeated measures
MRI	Magnetic resonance imaging
MTX	Methotrexate
NSAIDs	Non-steroidal anti-inflammatory drugs
PaGA	Patient's Global Assessment of disease activity
[redacted]	[redacted]
PSOC	Primary system organ classes
PCS	Physical component score
PD	Pharmacodynamic(s)
PFS	Prefilled syringe
PhGA	Physician's global assessment of disease activity
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PoC	Proof of concept
PPD	Purified protein derivative
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PsA	Psoriatic arthritis
PSD	Premature Subject Discontinuation
PSO	Psoriasis
PT	Prothrombin time
PUVA	Psoralen and ultraviolet A
q1w	every week
q4w	every 4 weeks
QMS	Quality Management System
RA	Rheumatoid Arthritis
RAP	Reporting & Analysis Process
RBC	Red Blood Cell(s)
RF	Rheumatoid Factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
s.c.	subcutaneous
sCR	serum creatinine
SD	Standard deviation
SF36-PCS	Short form health survey -physical component summary
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SJC	Swollen Joint Count
SUSAR	Suspected Unexpected Serious Adverse Reaction
t.i.d	3 times a day
TBL	Total bilirubin
TD	Study Treatment Discontinuation
TEAE	Treatment Emergent Adverse Events

TFLs	Tables, Figures, Listings
TFQ	Trial Feedback Questionnaire
TJC	Tender Joint Count
TNFα	Tumor Necrosis Factor alpha
ULN	Upper Limit of Normal
ULQ	Upper Limit of Quantification
UVA	Ultraviolet A
UVB	Ultraviolet B
VAS	Visual Analog Scale
WBC	White Blood Cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
WoCBP	Women of Childbearing Potential

1 Introduction

Data will be analyzed by Novartis according to this SAP and the data analysis Section 12 of the clinical 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.

This version of SAP covers the statistical and analytical plans of the CAIN457F2367 trial regarding the final DBL. Analyses pertaining to Week 16 will not be repeated.

1.1 Study design

This bridging study uses a randomized, double-blind, placebo-controlled, parallel-group design to assess the efficacy, safety, and tolerability of secukinumab 150 mg s.c. in Chinese participants with active PsA.

A screening period running up to 10 weeks before randomization will be used to assess participant eligibility followed by 52 weeks of treatment.

At BSL, approximately 40 Chinese participants whose eligibility are confirmed will be randomized to one of two treatment groups in 1:1 ratio:

- Group 1 – secukinumab 150mg s.c.:

Secukinumab 150 mg (1.0 mL PFS of 150 mg dose) administered at BSL, Weeks 1, 2, and 3 followed by dosing every four weeks starting at Week 4.

- Group 2 – placebo s.c.

Placebo (1.0 mL PFS) administered at BSL, Weeks 1, 2 and 3, followed by dosing every four weeks starting at Week 4.

At Week 16 the participants in Group 1 and Group 2 will be re-randomized in a blinded manner in 1:1 ratio separately.

- The participants in Group 1 will be re-randomized in 1:1 ratio to secukinumab 150 mg s.c. q4w regimen (1.0 mL PFS of 150 mg dose + 1.0 mL PFS of placebo) or secukinumab [redacted] s.c. q4w regimen ([redacted])
- The participants in Group 2 will be re-randomized in 1:1 ratio to secukinumab 150 mg s.c. q4w regimen (1.0 mL PFS of 150 mg dose + 1.0 mL PFS of placebo) or secukinumab [redacted] s.c. q4w regimen ([redacted])

Stratification is not applicable in the study.

A primary endpoint analysis was conducted after all participants complete Week 16 visit. Rescue medication was not allowed before the completion of Week 16 assessments (protocol Section 6.2.3). Although no participant will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, if rescue with prohibited biologics (as described in section 6.2.2) occurs prior to completion of Week 16 assessments, participants will be discontinued from the study treatment. Efficacy will be assessed in detail at every study visit, and participants who are deemed not to be benefiting from the study treatment based upon safety

and efficacy assessments by the investigator, or for any reason of their own accord, are free to discontinue participation in the study at any time.

A follow-up visit will be done 12 weeks after last study treatment administration for all participants, regardless of whether they complete the entire study as planned or discontinue prematurely.

The total combined duration of treatment for this Phase III study is 52 weeks.

1.2 Study objectives and endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate the treatment effect of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) in Chinese participants with active PsA is consistent with global population by assessing American College of Rheumatology 20 (ACR20) response rates in participants treated with secukinumab 150 mg s.c. compared to placebo s.c. at Week 16.	• ACR20 response at Week 16. A patient will be considered as improved according to the ACR20 criteria if he/she has at least 20% improvement in the three following measures: • Tender joint count; • Swollen joint count; • and at least 3 of the following 5 domains: a. Patient's assessment of PsA pain b. Patient's global assessment of disease activity c. Physician's global assessment of disease activity d. Health Assessment Questionnaire Disability Index (HAQ-DI©) score e. Acute phase reactant (hsCRP or ESR)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the efficacy of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) at Week 16 compared with placebo by assessing the proportion of participants achieving an ACR50 response.	• ACR50 response rate at Week 16.
• To evaluate the efficacy of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) at Week 16 compared with placebo by assessing the changes from baseline in Disease Activity Score for 28 joints (DAS28-CRP).	• Change from baseline in DAS28-CRP at Week 16.
• To evaluate the efficacy of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) at Week 16 compared with placebo by assessing change from baseline in PASDAS (Psoriatic Arthritis Disease Activity Score).	• Change from baseline in PASDAS at Week 16.
• To evaluate the efficacy of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) at Week 16 compared with placebo by assessing the changes	• Change from baseline in SF36-PCS at Week 16.

Objective(s)	Endpoint(s)
from baseline in medical outcome short form health survey (SF36-PCS).	
• To evaluate the efficacy of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) at Week 16 compared with placebo by assessing the changes from baseline in Health Assessment Questionnaire - Disability Index (HAQ-DI©).	• Change from baseline in HAQ-DI© at Week 16.
• To evaluate the overall safety and tolerability of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w).	• Physical examination, vital signs, laboratory values, AEs/SAEs.

[redacted]

2 Statistical methods

2.1 Data analysis general information

The primary endpoint analysis was performed after all participants complete Week 16. The Final analysis will be conducted when all participants have either withdrawn or completed the study. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Summary statistics for continuous variables will generally include the number of participants (N), mean, standard deviation (SD), minimum, lower quartile, median, upper quartile, and maximum. For binary or discrete variables, the absolute number of participants in each category and relative frequencies will be provided.

Unless otherwise specified, two-sided 95% confidence intervals will be displayed.

In case of a global health disruptive event, such as pandemic/epidemic (e.g., COVID-19), affecting the ability of the patient or the site to adhere to protocol requirements and assessments and therefore leading to a potential increase in the number of missing measurements, additional analysis populations may be defined as per the instructions and procedures outlined in Section 16.9 in the protocol.

The inferential efficacy evaluation of secukinumab relative to placebo was generally focus on the first 16 weeks of treatment unless otherwise specified.

Participants may be included in more than one treatment group for some analysis (e.g. exposure adjusted adverse events over the entire treatment period).

Note that the treatment groups for a participant may differ depending on the time period of the analysis and whether one assesses the participant for efficacy or safety.

Data may also be presented by a combination of the ‘original’ and ‘switch’ treatment groups. These treatment groups represent the treatment combinations the subjects experience over the course of the entire trial.

Efficacy data following re-randomization

Data will also be presented after Week 16, by a combination of the 'original' and 'switch' treatment groups and will be referred to as treatment sequence. These treatment sequences represent the treatment combinations the subjects experience over the course of the entire trial in case of re-randomization (refer to Section 2.1.1.1).

At the primary endpoint analysis, efficacy and safety data for the placebo-controlled period up to Week 16 were presented. Additional aspects of efficacy, safety and tolerability of secukinumab of the data collected up to the final database lock at the end of study will be investigated in the final analysis. Data collected after Week 16 will generally be summarized descriptively on the FAS population using treatment sequence.

2.1.1 General definitions

2.1.1.1 Treatment groups

In the final analysis, the summaries by treatment will be performed by the treatment sequence.

- Treatment sequence:
    - AIN457 150 mg – AIN457 150 mg
    - AIN457 150 mg – AIN457 [redacted]
    - Placebo – AIN457 150 mg
    - Placebo – AIN457 [redacted]

For some safety summaries (e.g., exposure-adjusted) the 'switch' treatment may be summarized separately:

- Entire study: Placebo, Any AIN457 150 mg, Any AIN457 [redacted], Any AIN457.

In the safety and efficacy listings, the groups will be presented by treatment sequence.

2.1.1.2 Study Day 1 and other study days

The first day of administration of randomized study treatment (first dose) is defined as Study Day 1 or Day 1.

All other study days will be labeled relative to Day 1. For event dates on or after Day 1, study day for a particular event date is calculated as [Date of event] – [Date of first dose] + 1, i.e., Day 2, Day 3, etc., will be one day, two days, etc., after Day 1, respectively. For the dates before Day 1, study day for an event date is calculated as [Date of event] – [Date of first dose], i.e., Day -1, Day -2, etc., will be one day, two days, etc., before Day 1, respectively. Duration of an event will be calculated as (Event end date – Event start date + 1).

The descriptor "Day 0" will not be used.

2.1.1.3 Screening, baseline and post-baseline definitions

Screening refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to the date of first dose of study treatment (for safety analysis) or prior to the randomization date (for efficacy analysis). Per protocol, subject informed consent must be obtained prior to performing any study related activity. The date of signing informed consent is the start date of screening period. Any assessment obtained during the screening period will be labeled screening assessment. Assessments made on Day 1 may occur before or after the randomization or the first dose. Further information will be found in Programming Datasets Specifications (PDS).

For efficacy analyses, baseline is the last assessment (including unscheduled visits) obtained (on or) before randomization (day). All assessments obtained after randomization (day) are considered as post-baseline unless otherwise specified.

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

Of note, baseline will be derived based on the randomization day or first dose day, exact randomization/dosing time is not considered.

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

2.1.1.4 Day of last dose of randomized study treatment

The date of last dose will be collected via the electronic case report form (eCRF). The subject's exposure will be calculated considering the end of treatment period visit (e.g., treatment completion visit). If a subject discontinued early, then the last dose + 84 days or the last visit during the follow-up period whichever occurs earlier is considered.

2.2 Analysis sets

The following analysis sets will be used in this study:

Randomized set: The randomized set will be defined as all participants who were randomized. Unless otherwise specified, mis-randomized participants (mis-randomized in IRT) will be excluded from the randomized set.

Mis-randomized participants are defined as those participants who were mistakenly randomized into the IRT prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomized participants are treated as screen failures.

Full analysis set (FAS): The FAS will be comprised of all participants from the randomized set to whom study treatment has been assigned. Following the intent-to-treat principle, participants will be evaluated according to the treatment assigned to at randomization.

Three subsets of FAS are defined as follows:

[redacted]

- Psoriasis subset: The psoriasis subset will include all FAS participants who have ≥ 3% of the BSA affected by psoriatic skin involvement at BSL.

Safety set: The safety set includes all participants who took at least one dose of study treatment during the treatment period. Participants will be evaluated according to treatment received.

2.2.1 Subgroup of interest

Not applicable.

2.3 Patient disposition, demographics and other baseline characteristics

Summary statistics will be presented for continuous demographic and BSL characteristic variables for each treatment sequence and for all participants in the randomized set. The number and percentage of participants in each category will be presented for categorical variables for each treatment group and all participants.

The following demographic variables and BSL disease characteristics, if collected, will be analyzed:

Continuous variables:

- Age
- Height
- Weight
- Body mass index (BMI) = (body weight in kilograms) / (height in meters)^2

Categorical variables:

- Age categories (<65 years, 65-74, 75 years and older)
- Gender
- Race
- Ethnicity
- Smoking status at baseline

The following disease specific baseline characteristics and history of disease will be summarized.

- Anti-TNF treatment history (naïve or inadequate responder), ACR components and other disease-related measures (e.g., DAS28, presense of dactylitis, presense of enthesitis, time

since first diagnosis of PsA, participant with psoriasis ≥ 3%), etc., number of prior biologic PsA therapies, dose of MTX or other DMARD at randomization.

Medical history

A history of PsA with focus on previous extra-articular involvement and past therapies for PsA will be obtained and summarized by treatment group for all patients in the Randomized set. Any other significant prior or active medical condition at the time of signing informed consent will be recorded and coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term.

Data on baseline and demographic characteristics will be summarized by treatment sequence at Final Analysis.

2.3.1 Patient disposition

The number of participants screened and the reasons for screen failures were presented in the previous primary endpoint analysis thus will not be repeated. The number and percentage of participants in the randomized set who completed the study periods and who discontinued from treatment or study prematurely (including the reason for discontinuation) will be presented at the end of each treatment period (e.g., Week 52 and entire treatment period), if appropriate, for each treatment sequence and all participants.

For each protocol deviation (PD), the number and percentage of participants for whom the PD applied will be tabulated by treatment sequence on the randomized set.

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

2.4.1 Study treatment / compliance

The analysis of study treatment data will be based on the safety set. The number of visits with active and placebo injections received will be presented by treatment group.

The duration of exposure to study treatment will also be summarized by treatment group. In addition, the number and percentage of participants 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 is defined as the time from first dose of study treatment to the time of treatment switch (for participants who switch treatment) or minimum of (last dose of the treatment + 84 days) and (last visit date). Participants who switch treatment during the study (e.g., from placebo to active treatment) will have exposure to both medications/doses using the appropriate start and stop dates.

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

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

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

2.4.2 Prior, concomitant and post therapies

Prior and concomitant treatments will be summarized in separate tables by treatment group for the safety set.

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit will be a concomitant medication, including those which were started pre-BSL and continued into the period where study treatment is administered.

Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of participants receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

Significant prior and concomitant non-drug therapies and procedures will be summarized by primary system organ class and WHODrug preferred term.

Prior surgeries and procedures are defined as surgeries and procedures done prior to first dose of study treatment. Any surgeries and procedures done between the day of first dose of study treatment and within the date of the last study visit will be a concomitant surgeries and procedures, including those which were started pre-BSL and continued into the period where study treatment is administered.

The number and percentage of participants receiving prior and concomitant PsA therapy will be presented by randomized treatment group as well as the reasons for stopping their therapies (primary lack of efficacy, secondary lack of efficacy, lack of tolerability, other) and the total duration of exposure to PsA therapies previously. NSAID, glucocorticoid and DMARD (MTX, Leflunomide, Sulfasalazine) use will be summarized.

Prior therapies have been summarized at Primary endpoint analysis; therefore, no summary tables or listings will be reproduced at the Final Analysis.

2.5 Analysis of the primary objective

The primary objective of this study is to assess the efficacy of secukinumab relative to placebo at week 16 based on the proportion of participants achieving an ACR20 response. The consistency of the treatment difference between this bridging study and the pooled efficacy data of global pivotal studies (CAIN457F2312, CAIN457F2318, CAIN457F2336 and CAIN457F2342) were evaluated at the Primary endpoint analysis and will not be repeated at the Final Analysis.

2.5.1 Primary endpoint

The primary efficacy variable was ACR20 response at Week 16. The analysis of the primary efficacy variable was 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.

The clinical question of interest is: What is the effect of secukinumab 150 mg s.c. versus placebo on the composite endpoint ACR20 response at Week 16 and the completion of 16 week− treatment in Chinese patients with active PsA?

The primary estimand is described by the following attributes:

a. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted PsA population

b. Variable: composite of remaining on the study and on randomized treatment through 16 weeks and achieving ACR20 response at 16 weeks

c. Treatment of interest: Secukinumab 150 mg s.c. and Placebo

d. Intercurrent event: the intercurrent event of discontinuation from treatment or study prior to Week 16 has been addressed via the composite variable definition

e. Population-level summary: difference in proportions of responders between secukinumab and placebo groups

The estimand of binary variables is (s.c. secukinumab regimen vs placebo) obtained from a logistic regression model with treatment as a factor and weight as a covariate at week 16 in the FAS population. Difference in marginal response proportions were computed for s.c. secukinumab regimen and placebo regimen utilizing the logistic regression model fitted. In the analysis subjects discontinued study drug, dropping out or being unblinded before week 16 or having missing response data at week 16 are considered as non-responders.

2.5.2 Statistical hypothesis, model, and method of analysis

The statistical hypothesis, model and method of analysis have been presented in the SAP for Primary endpoint analysis and will not be repeated in this document.

2.5.3 Handling of missing values/censoring/discontinuations

The handling of missing values has been presented in the SAP for Primary endpoint analysis and will not be repeated in this document.

2.5.4 Supportive analyses

The supportive analyses have been presented in the SAP for Primary endpoint analysis and will not be repeated in this document.

2.6 Analysis of the secondary objectives

2.6.1 Secondary endpoints

The secondary efficacy variables are described below. Secondary efficacy variables were analyzed using the FAS population. Handling of missing data for secondary variables were the same as for the primary variable.

- ACR50 response rate at Week 16

- Change from baseline in DAS28-CRP at Week16
- Change from baseline in PASDAS at Week 16
- Change from baseline in SF36-PCS at Week 16
- Change from baseline in HAQ-DI© at Week 16

The clinical questions of interest are:

- What is the effect of secukinumab 150 mg s.c. versus placebo on the composite endpoint ACR50 response at week 16 and the completion of 16 week-treatment in Chinese patients with active PsA?
- What is the effect of secukinumab 150 mg s.c. versus placebo on change from BSL in DAS28-CRP at week 16 in Chinese patients with active PsA had patients completed 16 week-treatment?
- What is the effect of secukinumab 150 mg s.c. versus placebo on change from BSL in PASDAS at week 16 in Chinese patients with active PsA had patients completed 16 week-treatment?
- What is the effect of secukinumab 150 mg s.c. versus placebo on change from BSL in SF-36 PCS at week 16 in Chinese patients with active PsA had patients completed 16 week-treatment?
- What is the effect of secukinumab 150 mg s.c. versus placebo on change from BSL in HAQ-DI at week 16 in Chinese patients with active PsA had patients completed 16 week-treatment?

The justification for targeting the treatment effect is that we wish to estimate the effect of the study drug for the full duration when administered without dose changes.

The estimand definition of all secondary objectives related to response (e.g., ACR50, ets.) will have the same attributes as that for the primary estimand, except for the variable of interest.

Estimand definition for the secondary continuous variables (e.g., HAQ-DI©, etc.) is the following:

a. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted PsA population

b. Variable: change from baseline in the variable of interest

c. Treatment of interest: Secukinumab 150 mg s.c. and Placebo

d. Intercurrent event: discontinuation from treatment or study prior to Week 16

e. Population-level summary: difference in variable means between secukinumab and placebo groups

2.6.2 Statistical hypothesis, model, and method of analysis

The statistical hypothesis, model and method of analysis have been presented in the SAP for Primary endpoint analysis and will not be repeated in this document.

2.6.3 Handling of missing values/censoring/discontinuations

The statistical hypothesis, model and method of analysis have been presented in the SAP for Primary endpoint analysis and will not be repeated in this document.

2.7 Safety analyses

Summaries will be performed for the entire treatment period on the Safety Set.

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

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

For those subjects who received not the treatment assigned at randomization, i.e., who received erroneously the wrong treatment at least once, an additional AE listing will be prepared displaying which events occurred after the treatment errors.

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

The safety variables to be analyzed include Adverse events (AEs)/Serious Adverse Events (SAEs), clinical laboratory tests (hematology, chemistry and urinalysis), physical examination results, ECGs, vital signs and deaths. Safety variables are to be tabulated by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum; or n and percent). No formal statistical testing is planned.

2.7.1 Adverse events (AEs)

Treatment-emergent adverse events (i.e., events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term and on or before last dose + 84 days) will be summarized.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of participants having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a participant reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a participant reported more than one adverse event within the same primary system organ class, the participant will be counted only once with the greatest severity at the system organ class level, where applicable. Serious adverse events will also be summarized.

These summaries may be presented separately by placebo controlled period and entire study.

As appropriate, the incidence of AEs will be presented per 100 patient years of exposure (exposure-adjusted incidence rates).

Separate summaries will be provided for death, serious adverse event, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment (including study treatment discontinuation).

A graphical display of relative frequencies within system organ classes and relative risks, as appropriate, will be presented.

Adverse events will also be reported separately by Standardized MedDRA Query (SMQ) according to MedDRA. The MedDRA version used for reporting the study will be described in a footnote.

Treatment emergent and non-treatment emergent adverse events will be listed.

Algorithms for date imputations will be provided in Programming Datasets Specifications.

For serious adverse events (SAEs) occurred during screening a listing were prepared for all subjects screened including screening failures at the primary endpoint analysis.

The safety analysis that will be performed for treatment emergent AEs and on treatment labs and vital signs for each analysis period is described in Table 2-1.

The data in the period of Day 1 – Week 16 were presented at the primary endpoint analysis; the data in the period of Entire treatment will be presented at the Final Analysis.

Table 2-1 Overview of analysis on some safety endpoints

Analysis period	AEs & SAEs	AEs-SMQ	AEs by severity	study drug related AEs	notables for (vitals/ ECG), lab criteria	Risk
Day 1 – Week 16	• crude incidence	• crude incidence	• crude incidence	• crude incidence	• crude incidence	• crude incidence
Entire Treatment	• crude incidence • exp.time adjusted incidence	• exp.time adjusted incidence	• crude incidence	• crude incidence	• crude incidence	• crude incidence • exp.time adjusted incidence

* Exposure-adjusted incidence rates will be done for the following:
At the PSOC for AE and SAE and Level 1 for Risks and SMQ analysis

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 incidence greater than 2% 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.

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 $\leq$ 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 of study treatment relationship will be provided by SOC and PT.

2.7.1.1 Adverse events of special interest / grouping of AEs

Safety topics of interest, such as risks defined in the Safety Profiling Plan (SPP), Risk Management Plan (RMP) or topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet.

Number and percentage of subjects with an event for SPP/RMP risks will be summarized.

2.7.2 Deaths

Separate summaries will be provided for deaths.

2.7.3 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 study treatment and on or before last dose +84 days.

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

For urinalysis, frequency tables will be presented. Specifically, the urine specific gravity will be presented in the following categories: <1.001, 1.001-1.005, 1.006-1.010, 1.011-1.015, 1.016-1.020, 1.021-1.025, 1.026-1.030, 1.031-1.035, >1.035. Descriptive summary statistics for the change from BSL to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from BSL will only be summarized for participants with both BSL and post BSL.

For each parameter, the maximum change from BSL within each study period will be evaluated analogously.

In addition, shift tables will be provided for all parameters to compare a participant's BSL 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 the BSL value was normal, low, or high. These summaries will be presented by laboratory test and treatment group. Shifts will be presented as well as for most extreme values post-BSL.

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in 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.

Table 2-2 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
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

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 up to week 16 or entire) analyzed. Of note, baseline will be defined as last assessment prior to first dosing in initial treatment phase.

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

- > 2.5 x ULN

Newly occurring or worsening liver enzyme abnormalities will also be summarized based on the event criteria given in Table 2-3:

Table 2-3 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 (Potential 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 data listing may be provided for subjects with abnormal laboratory data. Data of subjects with newly occurring or worsening liver enzyme abnormalities may be listed in an additional listing.

The laboratory values below Lower Level of Quantification (LLQ) or above Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ, respectively. The numerical part of the reported result will be treated as the actual LLQ or ULQ.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

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

Analysis in ECG parameters using descriptive summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by ECG parameter and treatment group. 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-BSL - BSL

The following quantitative variables will be summarized: ECG mean heart rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTc). Fridericia (QTcF) corrections will be presented for QTc.

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

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

Summary statistics will be presented for ECG variables by visit and treatment group.

In addition, 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.

A listing of all newly occurring or worsening abnormalities will be provided, as well as a by-subject listing of all quantitative ECG parameters.

Qualitative changes will be summarized.

2.7.4.2 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 of the vital sign measurements using summary statistics for the change from BSL for each post-BSL visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from BSL will only be summarized for participants with both BSL and post-BSL values and will be calculated as:

change from BSL = post-BSL – BSL

the number and percentage of subjects with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided in Table 2-4 below

Table 2-4 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

2.8 Patient-reported outcomes

SF-36

The following variables will be evaluated:

- SF-36 domain scores (based on a scale of 0-100)
- SF-36 PCS [redacted] scores (norm-based scores)
- [redacted]

For the change in SF-36 summary scores (PCS [redacted]), summary statistics will be provided using observed data for each treatment regimen.

[redacted]

The SF-36 domain scores will be summarized by treatment.

[redacted]

Patient's global assessment of disease activity (PaGA)

Summary statistics of observed data by visit and change from BSL in PaGA will be provided for each treatment.

Patient's assessment of PsA pain

Summary statistics of observed data by visit and change from BSL in Patient's assessment of PsA pain will be provided for each treatment.

[redacted]

2.10 Interim analysis

Interim analysis is not applicable in this study.

The primary endpoint analysis was performed after all participants have completed the Week 16 visit or discontinued earlier. The primary endpoint analysis was used for regulatory submission. The investigators, site personnel and monitors will continue to remain blinded to the original treatment assignment that each participant received at randomization until after the database lock for Week F60 analysis.

Subsequent to the primary endpoint analysis, the final analysis is planned after all participants have completed the Week F60 assessments and may be used for regulatory submission and/or publication purposes. Additional analyses may be performed to support interactions with health authorities, as necessary.

3 Sample size calculation

3.1 Primary endpoint(s)

As it is a bridging study for China registration, this study will pursue an estimation strategy rather than formal hypothesis testing of treatment difference.

Analysis of the pooled data of global pivotal studies (CAIN457F2312, CAIN457F2318, CAIN457F2336 and CAIN457F2342) showed an active drug response rate of about 51.4% and a placebo response rate of 23.1% after 16 weeks for ACR20. With 40 participants (1:1 ratio to two arms), there are approximately 86.0% probability to show at least 50% global treatment difference (14.15%) and approximately 96.0% probability to show positive treatment difference.

Table 3-1 shows the probability of success with different observed response rates.

Table 3-1 Probability of Success with Different Observed Response Rates

	Observed Response Rate				Criterion 1		Criterion 2	
	Secukinumab (p_1)	Placebo (p_2)	p_1-p_2	95% CI of (p_1-p_2)	Aimed Treatment Difference	PoS	Aimed Treatment Difference	PoS
Scenario 1	0.464	0.231	0.233	(-0.053, 0.519)	> 0.1415	0.772	> 0	0.922
Scenario 2	0.514	0.231	0.283	(-0.003, 0.569)	> 0.1415	0.860	> 0	0.960
Scenario 3	0.564	0.231	0.333	(0.048, 0.618)	> 0.1415	0.922	> 0	0.981
Scenario 4	0.614	0.231	0.383	(0.101, 0.665)	> 0.1415	0.961	> 0	0.992

4 Change to protocol specified analyses

In the protocol, Table 16-1 Clinically notable laboratory values and vital signs summarizes the criteria that will be used to define expanded limits and notable abnormalities of key laboratory tests. The notable BP levels defined in protocol are considered as severe clinical significance that may require follow-up action and reporting as appropriate. In this SAP we use the criteria as defined in Table 2-4. Therefore, the SAP will list all events that BP is out of normal range for reporting purpose.

5 Appendix

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.

5.1 Visit window

5.1.1 Visit window

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the Week 4 visit of a subject is delayed and occurs on Day 46 instead of on Day 29, say, it will be re-aligned to visit window Week 8. In case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified in Table 5-2.

For lab/ECG/vital signs, as for follow-up (F/U) visits, 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 (Week 60) or after nominal F/U visit date will be listed under label “Week 60” in the listing.

For chemistry, hematology, urinalysis and lipids, the F/U visit will be presented in the summary table to present long-term safety of AIN. Of note, participants are allowed to have gaps in visits. All data collected will be displayed in listings.

Table 5-1 Analysis visit windows

Analysis visit	Target Day	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	Group 9
Baseline	1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1
Week 1	8	2-11						2-11		
Week 2	15	12-18						12-18		
Week 3	22	19-25						19-25		
Week 4	29	26-43		2-43	2-43	2-57		26-43		
Week 8	57	44-71		44-71	44-71			44-71	2-85	
Week 12	85	72-99	2-99	72-99	72-99	58-99		72-99		
Week 16	113	100-127	100-155	100-141	100-141	100-141	2-239	100-127	86-141	2-239
Week 20	141	128-155						128-155		
Week 24	169	156-183		142-267	142-197	142-197		156-183	142-267	
Week 28	197	184-211	156-239					184-211		
Week 32	225	212-239			198-253	198-253		212-239		
Week 36	253	240-267						240-267		
Week 40	281	268-295	240-323		254-323	254-323		268-295		
Week 44	309	296-323						296-323		
Week 48	337	324-351						324-351		
Week 52	365	352-435	324-393	268-435	324-435	324-393	240-393	352-393	268-393	240-435

*The first administration of randomized study treatment (first dose) is defined as Day 1.
Group 1: ACR components, ESR, High sensitivity C-Reactive protein
Group 2: Hematology, blood chemistry, urinalysis
Group 3: SF-36 v2[redacted]
Group 4: [redacted], Patient's global assessment of psoriasis and arthritis disease activity (VAS)
Group 5: Pregnancy test
Group 6: ECG, Body weight
Group 7: Vital signs
Group 8: Lipids
Group 9: ANA, anti-dsDNA

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. Day 1 is the date of the first dose of randomized study treatment.

The mapping described above applies to all visits (not just scheduled visits). Repeat and/or unscheduled visits (which will be numbered in the database according to new NCDS standards) will be mapped for analysis purposes in the same way as scheduled visits. This leaves the possibility, then, for multiple measurements within an analysis window. If more than one assessment falls into the interval, the rules defined in Section 5.1.2 below are applied.

Re-randomization will be performed at the end of treatment period 1, assessment from treatment period 2 will not be considered for treatment period 1, e.g., if a Week 20 (scheduled visit) measurement would fall into the Week 16 visit window, this measurement would not be analyzed as treatment period 1 value. Of note, for subjects who discontinue in treatment period 1, i.e., not moving into treatment period 2, measurements taken in follow-up period would still be considered for treatment period 1.

5.1.2 Multiple assessments within visit windows

When there are multiple assessments in a particular visit window, the following rules are applied to select one value "representing" the subject in summary statistics in a visit window (See Table 5-2).

For baseline assessment definition, please see Section 2.1.1.3. For post-baseline visit windows, the following applies (unless otherwise specified)：

- for *quantitative variables*, the *closest* to the actual visit is chosen (if two assessments have the same distance, then the earlier one will be chosen);
- for *qualitative variables*, the *worst* record is selected. It is noted that in the analyses performed, *worst* case is always well defined (e.g., for urine protein values "+" and "++", the worst case is defined as "++"),
- in case qualitative variables are based on quantitative variables, [redacted], the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

Table 5-2 Rules for selecting values for analysis within a given visit window

Timing of measurement	Type of data	Rule
Baseline	All data	The last non-missing measurement made prior to or on the date of administration of the first dose of study treatment (the reference start date / Day 1). If a patient did not receive any dose of study treatment, then the randomization date will be used. Only date part is considered if just one assessment on Day 1. If there are multiple assessments on Day 1, following rules will apply: a. If assessment time exists, * select the last available measurement prior to reference start date/time considering time; * if no measurement prior to reference start data/time considering time, select the earliest measurement post reference start date/time considering time.

		b. If assessment time does not exist, select the available measurement from the lowest CRF visit number. For X-ray, a baseline value is the last measurement prior to dosing if available. Otherwise, take the first value within 30 days post dosing. For MRI, a baseline value is the last measurement prior to dosing if available. Otherwise, take the first value within 7 days post dosing.
Post-baseline efficacy	All data	For visits without switch of treatment in the window, the measurement closest to the target will be used. In the event two measurements are taken equally apart (e.g., 1 before target date and 1 after) the first one will be used. For visits during which the patient switches from placebo to AIN the following will be done based on whether or not the patient met the rescue criteria: a. if the analysis visit window is <= week 16, then - if available, the closest measurement to the target date which is ON or BEFORE the switch date will be used (i.e., the closest measurement to target which is on placebo) - if there are no data on or before the switch then the closest measurement to the target date after the switch will be used b. if the analysis visit window is > week 16, then - if available, the closest measurement to the target date which is AFTER the switch date will be used (i.e., the closest measurement to target which is on AIN) - if there are no data AFTER the switch then the closest measurement to the target date before the switch will be used Cases where the same parameter is recorded more than once on the same date will be handled as follows: * if time of completion exists the earliest measurement will be used; * if time does not exist the measurement from the lowest CRF visit number will be used
Post-baseline safety	Summary visit information (e.g., lab, ECG, etc.)	For visits without switch of treatment in the window, the measurement closest to the target will be used. In the event two measurements are taken equally apart (e.g., 1 before target date and 1 after) the first one will be used. For visits during which the patient switchers from placebo to AIN the following will be done based on whether or not the patient met the rescue criteria: a. if the analysis visit window is <= week 16, then - if available, the closest measurement to the target date which is ON or BEFORE the switch date will be used (i.e., the closest measurement to target which is on placebo) - if there are no data on or before the switch then the closest measurement to the target date after the switch will be used b. if the analysis visit window is > week 16, then - if available, the closest measurement to the target date which is AFTER the switch date will be used (i.e., the closest measurement to target which is on AIN) - if there are no data AFTER the switch then the closest measurement to the target date before the switch will be used Cases where the same parameter is recorded more than once on the same date will be handled as follows:

		* if time of completion exists the earliest measurement will be used; * if time does not exist the measurement from the lowest CRF visit number 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.

5.2 Description of efficacy variables

5.2.1 American College of Rheumatology (ACR) response

A participant is defined as an ACR20 responder if, and only if, the following three conditions hold:

- they have a ≥ 20% improvement in the number of tender joints (based on 78 joints)
- they have a ≥ 20% improvement in the number of swollen joints (based on 76 joints)
- they have a ≥ 20% improvement in three of the following five domains:
  - Patient's global assessment of disease activity (PaGA) (measured on a VAS scale, 0-100)
  - Physician's global assessment of disease activity (PhGA) (measured on a VAS scale, 0-100)
  - Patient's assessment of PsA pain (measured on a VAS scale, 0-100)
  - Health Assessment Questionnaire – Disability Index (HAQ-DI©) score
  - Acute phase reactant (hsCRP or ESR)

ACR50 = 50% improvement in at least 3 of the 5 measures and 50% improvement in the swollen and tender joint count.

[redacted]

5.2.1.1 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. [redacted]

[redacted]. These aspects are to be implemented during data capture and will not be addressed during programming.

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).

Data is recorded for tender and swollen joints (right or left side), i.e., a box (yes, no or not applicable) needs to be ticked for all joints.

5.2.1.2 Patients' global assessment of disease activity

The patient's global assessment of disease activity will be performed using a Visual Analog Scale (VAS) of 100 mm ranging from "0 -very good" to "100= 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 today'.*

5.2.1.3 Physicians' global assessment of disease activity

The PhGA 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 participant.

5.2.1.4 Patients' 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'.*

5.2.1.5 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 of the HAQ-DI©

The HAQ-DI© will be scored in accordance with the Alternative Disability Index (ADI) scoring as described in Wolfe F (2001), Zandbelt et al (2001) and the HAQ instruction [10]. The use of ADI scoring is due to how the data was collected for the "use of aids, devices, or help from

another person" questions. The ADI scoring does not include data collected from "use of aids, devices, or help from another person" questions in the calculation of scores. The ADI is one of the two disability indices described in HAQ instruction, to reflect the disability level of a subject when using aids and devices to compensate for disability. The HAQ-DI© using ADI scoring method was efficient and sensitive to change, and performed well to detect mild functional loss (Wolfe F, 2001).

The following coding is to be used for the 20 items of the 8 categories of the disability outcome dimension:

Without ANY Difficulty	0
With SOME Difficulty	1
With MUCH Difficulty	2
UNABLE to do	3

The score for each category will be the single response of the item with the highest score (greatest difficulty) within that category. For example, in the "Arising" category, there are two items: 1. "Are you able to stand up from a straight chair"; 2. "Are you able to get in and out of bed". If "Are you able to stand up from a straight chair" is marked as "3" and "Are you able to get in and out of bed" is marked as "0", then the score for the "Arising" category would be "3".

Therefore, the highest score reported by the subject for any component question of the eight categories determines the score for that category. If a component question is left blank, then the score of that category will be determined by the remaining completed question(s).

An ADI is computed by summing the computed scores for each category and then divided by the number of categories answered. The ADI is not computed if the subject does not have scores for at least 6 categories. The ADI is the HAQ-DI© score, which will be used in the statistical analyses of this instrument, e.g., ACRn calculation, HAQ-DI© change from baseline. The range for HAQ-DI© score is (0, 3).

HAQ-DI© response is defined by an improvement of at least 0.35 score points compared to baseline.

5.2.1.6 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 BSL only. The hsCRP results from samples collected during the treatment period will be revealed following database lock only.

5.2.1.7 Erythrocyte sedimentation rate (ESR)

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

Local ESR test will be performed.

5.2.2 DAS28 and EULAR response

DAS28, low disease activity and remission

The Disease Activity Score (DAS) is a combined index to measure the disease activity in patients with RA. It has been extensively validated for its use in clinical trials in combination with the EULAR response criteria.

The DAS28 is a measure of disease activity based on Swollen and Tender Joint Counts, CRP or ESR, and the Patient Global Assessment of PsA disease activity.

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(TJC28) + 0.28*sqrt(SJC28) + 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 primarily used for the interpretation of the outcome; DAS-ESR is considered supportive.

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.

EULAR response

Using the DAS, several thresholds have been developed for high disease activity, low disease activity or remission. Also, response criteria have been developed based on the DAS, so when the DAS of a patient is measured at two time-points (e.g., before the start of a treatment and after 3 months), the patient's clinical response can be assessed.

Comparing the DAS28-CRP (or ESR) from one patient on two different time-points, it is possible to define improvement or response. The EULAR response criteria are defined as follows:

Table 5-3 EULAR response criteria

Present DAS28	DAS28 improvement		
	>1.2	0.6-1.2	<0.6
<3.2	Good response	Moderate response	No response

3.2-5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

Both the thresholds for high and low disease activity and remission and the above mentioned improvement criteria are used to interpret the DAS28 scores.

5.2.3 Psoriatic Arthritis Disease Activity Score (PASDAS)

PASDAS is a new composite measure developed to access disease activity in Psoriasis (GRACE Project) (Helliwell et al 2012). It is calculated by utilizing seven measures; the seven components are: Patient reported measures [redacted] skin, peripheral joint counts (Tender and Swollen joint counts), [redacted] acute phase response (CRP) and Patient & Physician global VAS scores.

PASDAS = (0.18 x √Physician global VAS)

+ (0.159 x √Patient global VAS)

− (0.253 x √SF36-PCS)

+ (0.101 x LN (Swollen joint count + 1)

+ (0.048 x LN (Tender joint count + 1)

[redacted]

+ (0.102 x LN (CRP + 1)) + 2)*1.5

If any component measurement is missing, PASDAS will be missing. The patient global VAS defined in the PASDAS score is “VAS for PASDAS assessment” which measures patient’s global assessment of PSORIASIS and ARTHRITIS disease activity. The Physician global VAS is the Physician’s global assessment of PsA disease activity. Tender Dactylitis count is from “Leeds Dactylitis Instrument” CRF page with “Was dactylitis present?” = “Yes” and “Tender/non-tender” = “Tender”.

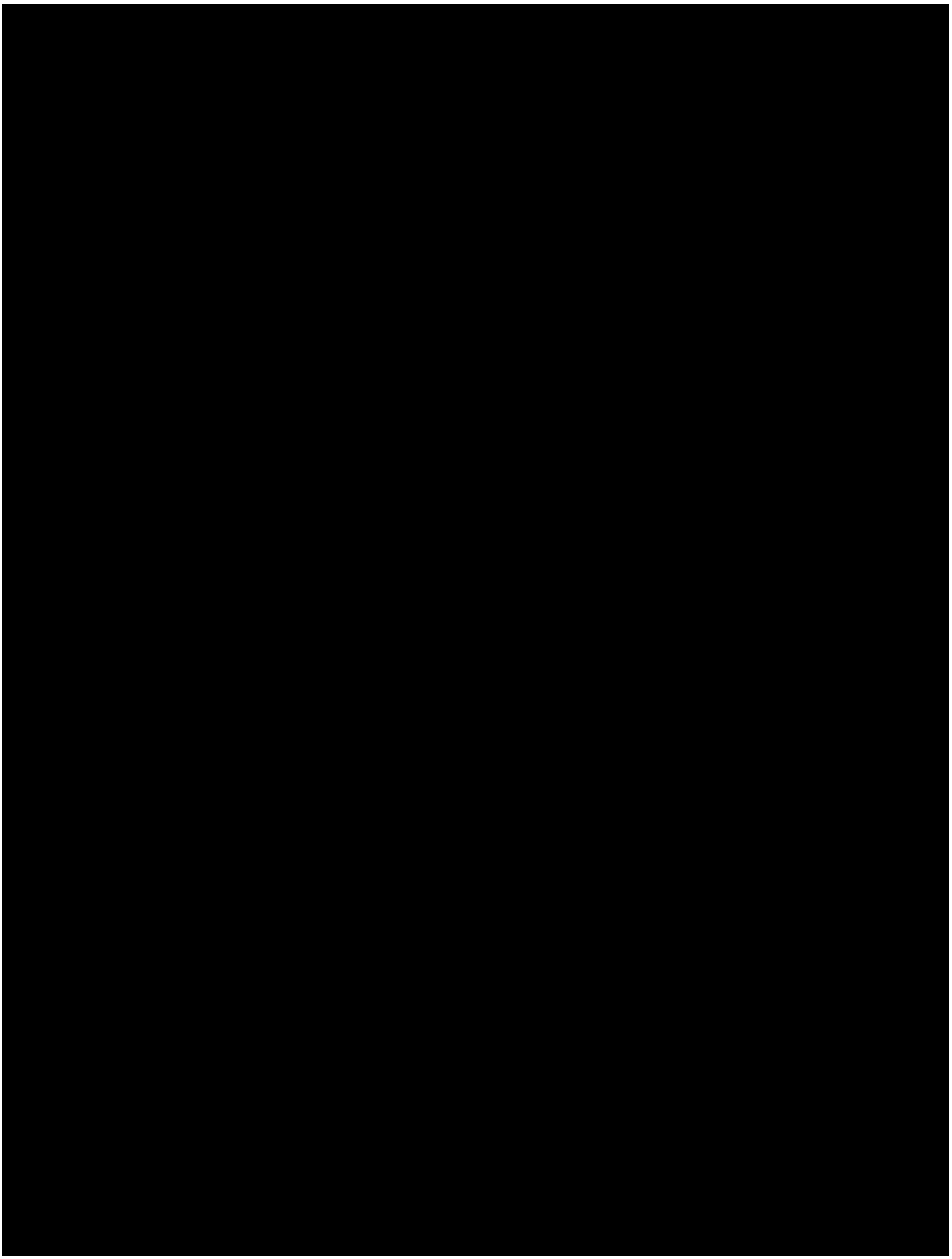
66-swollen / 68-tender joint counts for PASDAS assessment:

There are only 66 swollen and 68 tender joint counts which will be used for PASDAS assessment. That is the 10 joints in CRF: CMC1, DIP2 (FOOT), DIP3 (FOOT), DIP4 (FOOT), and (DIP5 (FOOT) both left and right, should not be counted in the swollen/tender joint count in PASDAS formula.

If the number of joints for which data were available (e.g., T) is less than 66/68 for the swollen/tender joint assessment, the number of swollen/tender joints (e.g., t) will be scaled up proportionately (i.e., 66*t/T or 68*t/T for swollen or tender joint count).

5.2.3.1 VAS for PASDAS assessment

Global Disease Activity: The patient's assessment of psoriasis and arthritis will be performed using 100 mm VAS ranging from 'Excellent' to 'Poor' after the question *'Considering all the ways PSORIASIS and ARTHRITIS affects you, please indicate with a vertical mark (|) through the horizontal line how well you are doing over the past week'*.



5.3 Imputation rules

5.3.1 Study drug

Any partial dates will be imputed as follows:

We take the earlier day of

- The last day in the month and
- The end day of the corresponding epoch

5.3.2 AE date imputation

Impute AE end date:

1. If the AE end date 'month' is missing, the imputed end date should be set to the earliest of the (min (last visit date, last dose data + 84 days), 31DECYYYY, date of death).
2. If the AE end date 'day' is missing, the imputed end date should be set to the earliest of the (min (last visit date, last dose date + 84 days), last day of the month, date of death)
3. If AE 'year' is missing or AE is ongoing, the end date will not be imputed.

Impute AE start date:

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min(informed consent date, earliest visit date).

2. Else AE start reference date = treatment start date

1. If the AE start date 'year' value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.

2. If the AE start date 'year' value is less than the treatment starts date year value, the AE started before treatment. Therefore:

a. If AE 'month' is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).

b. Else if AE 'month' is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).

3. If the AE start date year value is greater than the treatment starts date year value, the AE started after treatment. Therefore:

a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).

b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

4. If the AE start date year value is equal to the treatment start date year value:

a. And the AE month are missing the imputed AE start date is set to the AE reference start date + 1 day.

b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).

c. Else if the AE month is equal to the treatment start date month or greater than the treatment starts date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.3.3 Concomitant medication date imputation

Impute CM end date:

1. If CM end day is missing and CM month/year are non-missing, then impute CM day as the minimum of treatment end date and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing, then impute CM day as the minimum of treatment end date and the end of the year (31DECYYYY).
3. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

Impute CM start date:

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment starts date year value, the CM started before treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JULYYYY)
    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY)
3. If the CM start date year value is greater than the treatment starts date year value, the CM started after treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the year start point (01JANYYYY)
    b. Else if the CM month is not missing, the imputed CM date is set to the month start point (01MONYYYY)
4. If the CM start date year value is equal to the treatment start date year value:
    a. And the CM month is missing, or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date
    b. Else if the CM month is less than the treatment starts date month, the imputed CM start date is set to the mid-month point (15MONYYYY)
    c. Else if the CM month is greater than the treatment starts date month, the imputed CM start date is set to the month start point (01MONYYYY)

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.3.3.1 Prior therapies date imputation

See Section 5.3.2.

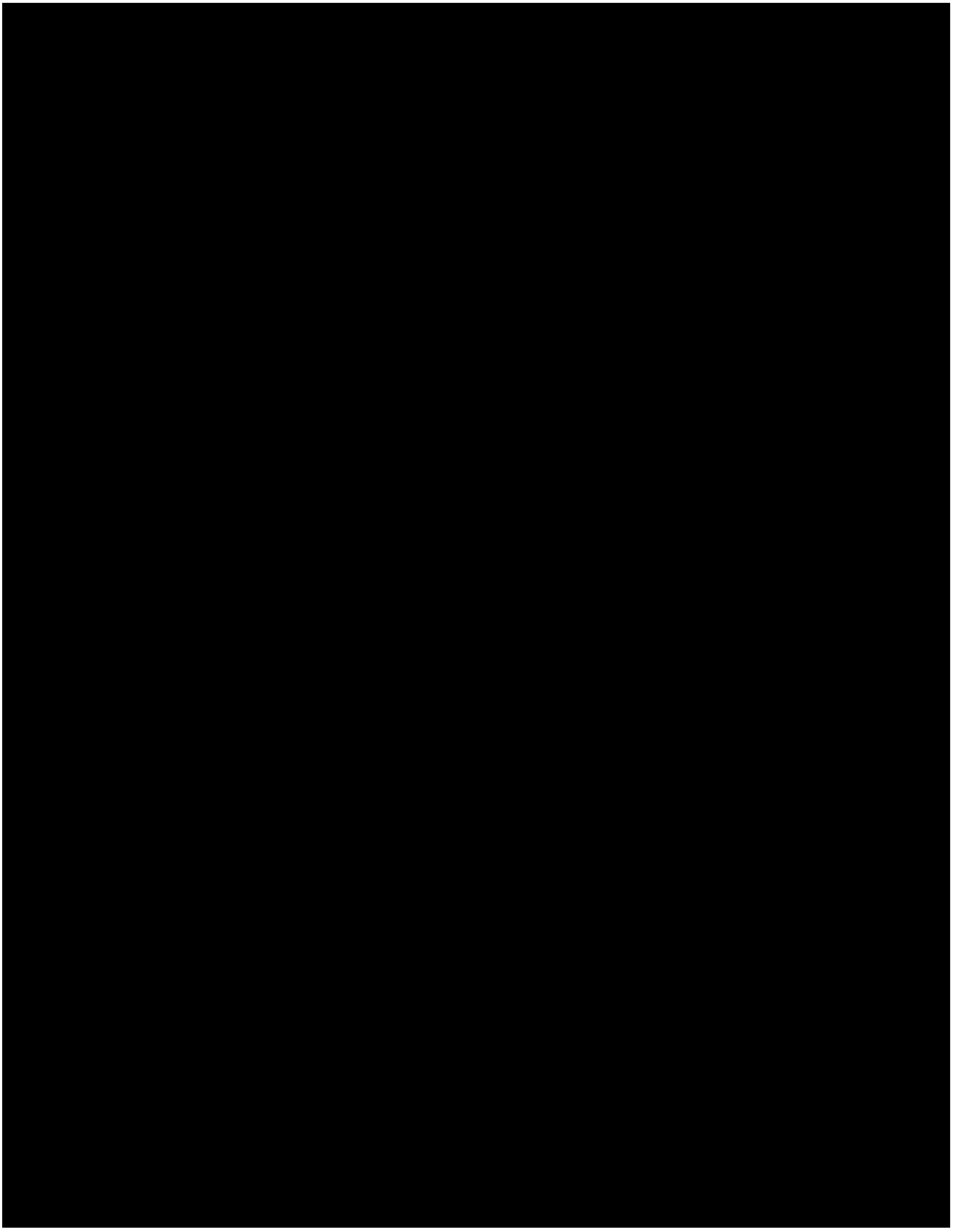
5.3.3.2 Post therapies date imputation

See Section 5.3.3.

5.3.3.3 Other imputations

5.4 AEs coding/grading

Adverse events will also be coded according to MedDRA dictionary, using a narrow search. The MedDRA version used for reporting the adverse events will be described in a footnote. 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.



[redacted]

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