NOVARTIS

Clinical Development

ACZ885/Canakinumab

ACZ885G1302 / NCT04717635

An open-label, single-arm, active-treatment study to evaluate efficacy and safety of canakinumab (ACZ885) administered for at least 48 weeks in Japanese patients with Adult Onset Still's Disease (AOSD)

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse Event
CRF	Case Report Form
CSR	Clinical Study Report
DMS	Document Management System
FAS	Full Analysis Set
IA	Interim Analyses
LLN	Lower Limit of Normal
LLQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Drug Regulatory Affairs
OMU	Original Measurement Unit
PK	Pharmacokinetics
CCI	[redacted]
RAP	Reporting & Analysis Process
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SMQ	Standardized MedDRA Queries
TFLs	Tables, Figures, Listings
ULN	Upper Limit of Normal
ULQ	Upper Limit of Quantification
WHO	World Health Organization

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of statistical analyses planned in the study protocol, and to provide detailed statistical methods that will be used for the Clinical Study Report (CSR) of study CACZ885G1302.

Data will be analyzed according to the data analysis Section 12 of the study protocol which will be available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and additional details will be provided, as applicable, in Appendix 16.1.9 of the CSR.

This SAP covers statistical and analytical plans for the primary efficacy analysis based on the data up to the time when the first 11 participants have reached Week 28 (or prematurely discontinued prior to Week 28), a 28 Week interim analysis after all participants have completed Week 28, a 48 Week interim analysis after all participants have completed Week 48 and the final analysis after all participants have completed the study.

The following documents was referenced while writing this SAP:

- Study protocol: Clinical Trial Protocol CACZ885G1302 version 03 dated 19-May-2023
- Case Report Forms:
  CACZ885G1302_Unique Blank eCRF Layout_Version 4.0
  CACZ885G1302_Expanded Blank eCRF Layout_Version 4.0
  CACZ885G1302_Annotated eCRF layout_Version 4.0

1.1 Study design

This study is an open-label, single-arm active treatment study to evaluate efficacy, safety, tolerability and PK/PD of canakinumab 4 mg/kg (maximum of 300 mg) every four weeks subcutaneously administered for at least 48 weeks in Japanese participants with AOSD until canakinumab is approved and commercially available for AOSD in Japan or Novartis terminates the study. Approximately 21 participants will be enrolled in the study.

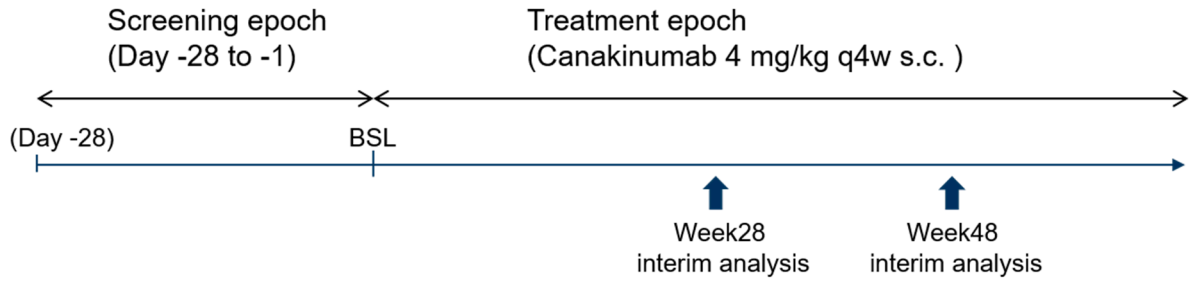
The study will consist of two distinct study epochs as outlined below (see also Figure 1-1):

- Screening epoch: Day -28 to Day -1
- Open label treatment epoch: Day 1 to approval and commercially available or study termination, whichever comes first.

Two interim analyses will be performed for this study - first IA after all participants have completed Week 28 to support the registration dossier, and second IA at Week 48 to supplement the dossier with long-term safety and efficacy data. At the interim analysis at Week 28, the primary efficacy analysis will be conducted based on the data up to the time when the first 11 participants have reached Week 28 (or prematurely discontinued prior to Week 28), CCI [redacted]

Final analysis will be performed after all participants have completed the study.

Figure 1-1 Study design



The primary efficacy analysis using the data up to the time when the first 11 participants have reached Week 28 (or prematurely discontinued prior to Week 28) will be performed at Week 28 interim analysis.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the efficacy of canakinumab with respect to the adapted ACR 30 response after 8 weeks treatment	• Proportion of participants who achieve adapted ACR 30 response at Week 8
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate ability of canakinumab to taper corticosteroids based on success criteria starting from Week 8 to Week 28	• Proportion of participants who are able to taper corticosteroids based on success criteria at Week 28.
• To evaluate the efficacy of canakinumab with respect to the adapted ACR 30/50/70/90/100 response over time	• Proportion of participants who achieved adapted ACR 30/50/70/90/100 response criteria at Day 15 and all subsequent visits.
• To evaluate the efficacy of canakinumab on the systemic feature score over time	• Change from baseline in Systemic Feature Score (total score and each components) at Day 15 and all subsequent visits.
• To evaluate the efficacy of canakinumab with respect to the components of adapted ACR criteria over time	• Change from baseline in each component of adapted ACR at Day 15 and all subsequent visits
• To evaluate ability of canakinumab to taper corticosteroids dose over time after Week 8	• Change from baseline of corticosteroid dose at all visits after Week 8.
• To evaluate the efficacy of canakinumab on rash over time	• Presence of rash (typical/atypical) at all visits during study.
• To evaluate the efficacy of canakinumab on DAS28-CRP	• Change from baseline in DAS28-CRP at Day 15 and all subsequent visits.
• To assess the safety and tolerability of canakinumab	• Incidence and severity of Treatment Emergent AEs. Proportion of participants up to end of study with:

Objective(s)	Endpoint(s)
	- Adverse events - Serious adverse events - AEs related to study drug - AEs leading to discontinuation
	• Means and mean change over time of: -Vital sign parameters -Laboratory parameters
• To evaluate the pharmacokinetics (PK) / pharmacodynamic (PD) of canakinumab	• Canakinumab concentrations over time • Total IL-1β (sum of IL-1β free and bound to canakinumab) level s over time
• To assess the immunogenicity of canakinumab	• Anti-canakinumab antibody identification and titer at BSL, Week 24, Week 48 and every 24 weeks until EOS.
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
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Successful oral corticosteroids tapering is defined as meeting one of the following in terms of prednisone equivalent dose per day (mg/kg/day).

- Participants with prednisone equivalent dose of > 0.8 mg/kg/day at baseline were able to reduce their dose to ≤ 0.5 mg/kg/day.
- Participants with prednisone equivalent dose from ≥ 0.5 mg/kg/day and ≤ 0.8 mg/kg/day at baseline were able to reduce their dose by at least 0.3 mg/kg/day.
- Participants with any initial prednisone equivalent dose at baseline were able to reduce their dose to ≤ 0.2 mg/kg/day.
- Participants with prednisone equivalent dose of ≤ 0.2 mg/kg/day at baseline were able to reduce their dose with any reduction.

AND maintaining a minimum adapted ACR30 response.

Details on how to calculate the prednisone equivalent dose per day are given in Section 5.6.1.

Unless otherwise stated, the terms “prednisone equivalent dose” means prednisone equivalent dose of oral steroids.

2 Statistical methods

2.1 Data analysis general information

The statistical analysis will be performed by Novartis using SAS 9.4 TS Level 1M6 or above.

Summary statistics for continuous variables will generally include n, mean, standard deviation, median, minimum, and maximum. For categorical variables, this will generally include frequency and percentage. For selected parameters, 25th and 75th percentiles will also be presented when applicable.

The data cut-off date for Week 28/Week 48 IA will be the date of Week 28/Week 48 visit for the last participant. For efficacy analyses, the data up to Week 28/Week 48 visit for each individual participant will be included. For safety analyses and summaries for treatments, all available data will be included.

No center-specific or stratified analyses will be performed.

2.1.1 General definitions

Study treatment

Study treatment refers to subcutaneous injection of canakinumab (ACZ885).

Date of first/last administration of study treatment

Date of first/last administration of study treatment is the date that the participant is first/last administered study treatment.

Study day

For efficacy and safety assessments, study day will be calculated relative to Day 1, the first dose day.

If Date of assessment ≥ Day 1 date,

Study Day = Date of assessment – Day 1 date + 1

If Date of assessment < Day 1 date,

Study Day = Date of assessment – Day 1 date

Baseline

Baseline is the last assessment (including screening visits and unscheduled visits) obtained before the first administration of the study treatment.

On-treatment period

Treatment period is from the date of first administration of study treatment to the end of study (EOS) for each participant.

2.1.2 Analysis visit

In the analysis of each visit, analysis visit is required to specify the time point to be analyzed. The visit name as reported in the eCRF will be used except for the end of study (visit name = EOS), which will be mapped according to Table 2-1.

Table 2-1 Visit window

Protocol defined			Time point to be analyzed	Visit window (days) for mapping end of study visit
Epoch	Week	Day		
Screening	-4	-28 to -1	Baseline	-28 to -1
Open-label treatment	1	1	Baseline	1
	1	3	Day 3	2-4
	2	15	Day 15	5-16
	4	29	Week 4	17-31
	8	57	Week 8	32-60
	12	85	Week 12	61-88
	16	113	Week 16	89-116
	20	141	Week 20	117-144
	24	169	Week 24	145-172
	28	197	Week 28	173-200
	32	225	Week 32	201-228
	36	253	Week 36	229-256
	40	281	Week 40	257-284
	44	309	Week 44	285-312
	48	337	Week 48	313-340
	Every 4 weeks after Week 48	X	Every 4 weeks after Week 48	(X-24) – (X+3)

2.2 Analysis sets

The Full Analysis Set (FAS) and Safety set comprise all participants who received at least one dose of study treatment. (See Section 5.5 for the rule of exclusion criteria of analysis sets).

The number of participants who are included in the FAS and the Safety set will be provided.

2.2.1 Subgroup of interest

Adapted ACR30/50/70/90/100 analysis (see primary analysis and secondary analysis), key secondary analysis, and summary of treatment emergent AEs by SOC and PT will be performed by the following subgroups:

- Baseline age (at screening): <65, ≥65 years
- Prior use of Tocilizumab: Yes, No
- Sex: Male, Female
- Weight group: ≤50, >50-≤75, >75 kg

The subgroup based on prior use of Tocilizumab (Yes, No) will be used to perform the additional subgroup analyses for Week 28 IA as follows:

- Adapted ACR 30/50/70/90/100 response by visit
- Oral corticosteroid dose by visit
- Each adapted ACR components by visit
- Rash by visit
- DAS28-CRP by visit
- Systemic feature score: Total score by visit
- Systemic feature score: Each component score by visit
- Number of tender joints
- Number of swollen joints

The subgroup analyses described above based on the subgroup of prior use of Tocilizumab will be performed only for the first 11 participants.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of participants screened, completed screening epoch, and discontinued screening epoch with the reasons for screen failures will be provided.

The number and percentage of participants in the safety set who completed treatment epoch and who discontinued treatment epoch prematurely with the reasons will be presented. At a 28 week analysis or a 48 week analysis, the number and percentage of participants in the safety set who completed Week 28 or Week 48 visit will be presented as completing treatment epoch for the interim analyses.

For each protocol deviation, the number and percentage of participants for whom the deviation applies will be tabulated for the Safety set.

The FPFV and LPLV dates, the number of participants who had IC, treated, discontinued and had AEs related to study treatment will be provided by center at a 28 week analysis for all participants.

2.3.2 Demographics and other baseline characteristics

The following common demographic variables will be summarized and listed for the FAS. The threshold used to convert continuous values to categorical variables may change depending on the obtained data.

Continuous variables:

- Age (years)
- Height (cm)
- Weight (kg)
- Body mass index (BMI)

Body Mass Index (*BMI*) will be calculated when both height and weight are available, using the following formula:

$$BMI = (\text{body weight in kilograms}) / (\text{height in meters})^2$$

Categorical variables:

- Age categories (<18, ≥18-<45, ≥45-<65, ≥65)
- Weight categories (≤50, >50-≤75, >75)
- Sex
- Race
- Race as collected
- Ethnicity

The following disease history and baseline characteristics will be summarized for the FAS.

Continuous variables:

- Body temperature (°C)
- Time from AOSD diagnosis to study entry (screening visit) (years)
- Standardized C-reactive protein (CRP)[*1] (mg/L)
- Oral prednisone equivalent dose at baseline (mg/day)
- Oral prednisone equivalent dose at baseline (mg/kg/day)
- Physician's global assessment of disease activity (VAS) (mm)
- Participant's assessment of disease activity (Participant's overall well-being) (VAS) (mm)
- Participant's assessment of disease activity (Pain) (VAS) (mm)
- Number of active joints (68 joints evaluated for pain/tenderness and 66 for swelling)[*2]

- Number of tender joints
- Number of swollen joints
- HAQ functional ability score
- DAS28-CRP
- CCI [redacted]
- Systemic feature score
- Ferritin (ug/L)

*1 Standardized C-reactive protein (CRP) (mg/L) will be calculated based on the SI normal range of 0.0-10.0 mg/L using the following formula:
Standardized CRP = 10 × [(observed CRP value – minOMU)/rangeOMU],
where minOMU and rangeOMU are minimum value and range of normal range on the original measurement unit respectively.
*2 The number of active joints is defined as the number of joints that are tender or swollen.

Categorical variables:

- Oral prednisone equivalent dose at baseline (0, >0-≤0.2, >0.2-<0.5, ≥0.5-≤0.8, >0.8 mg/kg/day)
- Rash* (Yes, No)
- Intermittent fever due to AOSD (Yes, No)
- Prior use of any biologics** (Yes, No)
- Prior use of Tocilizumab (Yes, No)

For the chest X-ray assessment at screening, a listing of participants having a positive result will be listed by participant.

*Rash is defined by the presence of typical salmon-pink rash on the trunk and elsewhere during the febrile episodes.

**Anakinra, Rilonacept, Tocilizumab, Etanercept, Infliximab, Golimumab, Adalimumab, Abatacept, Rituximab, Certolizumab, and etc.

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

2.4.1 Study treatment / compliance

The exposure to study drug (number of injections), duration of exposure (days) and total exposure in patient years will be summarized and listed for the Safety set. The number and percentage of participants of certain durations (any exposure, ≥4 weeks (28 days), ≥12 weeks (84 days), ≥24 weeks (168 days), ≥36 weeks (252 days), ≥48 weeks (336 days), etc.) will be provided.

For the interim analyses, the duration of exposure (days) for the continuation participants will be calculated as:

Duration of exposure (days) = the day of cut-off – the day of first dose of study treatment + 1.

For the interim analyses, the duration of exposure (days) for the discontinuation participants will be calculated as:

Duration of exposure (days) = the day of the last study visit – the day of first dose of study treatment + 1.

For the final analysis, the duration of exposure (days) will be calculated as:

Duration of exposure (days) = the day of the last study visit – the day of first dose of study treatment + 1.

The total exposure in patient years will be calculated as the total patient days divided by 365.25.

2.4.2 Prior, concomitant and post therapies

The number and percentage of participants taking prior medication, concomitant medication will be summarized in separate tables by preferred term and Anatomical Therapeutic Classification (ATC) class for the Safety set. Corticosteroids will be summarized separately from other medications. For concomitant medication, the above summary will be performed using the data up to Week 28/Week 48 visit in addition to all available data at the time point for the analyses.

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

In addition, the number and percentage of participants using non-drug therapies and procedures prior to and after the first dose of study treatment will be summarized by primary system organ class and preferred term. For non-drug therapies and procedures after the first dose of study treatment, the above summary will be performed using the data up to Week 28/Week 48 visit in addition to all available data at the time point for the analyses.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary clinical question of interest is: What is the benefit of Canakinumab in achieving clinical improvement for Japanese AOSD participants without increased use of corticosteroids regardless of study treatment discontinuations for any reason?

The justification for the primary estimand is that it will capture the actual effect of canakinumab in the condition that participants use stable dose of corticosteroids.

The primary estimand is described by the following attributes:

1. Population: Japanese AOSD participants.
2. Endpoint: Adapted ACR 30 response at Week 8
3. Treatment of interest: canakinumab 4 mg/kg s.c. (maximum of 300 mg) with stable dose of corticosteroids.

Handling of remaining intercurrent events:

1. Systemic corticosteroid dose increase and/or iv corticosteroid use before Week 8 (i.e. between baseline and Week 8 visit) for any reason: consider as non-response (Composite variable strategy)
2. Study treatment discontinuation for any reason: ignore (if adapted ACR 30 at Week 8 is available, it will be included in the analysis) (Treatment policy strategy)

The summary measure: Proportion of participants who achieve adapted ACR 30 at Week 8

The primary efficacy analysis will be based on the data up to the time when the first 11 participants in the FAS have reached Week 28 (or prematurely discontinued prior to Week 28).

Adapted ACR 30 criteria

The adapted ACR 30 response derived by ePRO vender will be used in the analysis.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary objective will be achieved if the null hypothesis is rejected at the 2.5% one-sided level of significance.

H0:pACZ $\leq$ 0.40 vs. HA:pACZ > 0.40,

with pACZ being the proportion of participants who achieved adapted ACR 30 at Week 8.

Frequency tables with the number and percentage of participants who achieved adapted ACR 30 response together with a 95% confidence interval will be provided based on the FAS. A binomial test using the normal approximation will be performed and the Wald asymptotic confidence interval with continuity correction will be presented. For hypothesis testing, one sided p-value will be presented.

2.5.3 Handling of remaining intercurrent events of primary estimand

The primary analysis will account for different intercurrent events as explained in the following:

Systemic corticosteroid dose increase and/or iv corticosteroid use before Week 8 for any reason

Composite variable strategy is applied to this intercurrent event. If a participant had corticosteroid dose increase and/or iv corticosteroid use during the first 8 weeks after study treatment start, he/she will be considered as non-responder at Week 8 regardless of whether adapted ACR 30 assessment is available (non-responder imputation).

Discontinuation of study treatment before Week 8 for any reason

Treatment policy strategy is applied to this intercurrent event. When a participant discontinued study treatment before Week 8, but adapted ACR 30 assessment at Week 8 is available, it will be included in the analysis.

2.5.4 Handling of missing values/censoring/discontinuations

Missing adapted ACR 30 assessment at Week 8 will be imputed with non-responder regardless of the reason for missing data (non-responder imputation).

2.5.5 Supplementary analyses

All of the supplementary analyses defined below will be based on the FAS.

The supplementary clinical question of interest is: What is the benefit of Canakinumab in Japanese AOSD patients to improve systemic and articular manifestation of AOSD regardless of systemic corticosteroid dose increase and/or intravenous administration of corticosteroid and regardless of treatment discontinuations for any reason? In this supplementary estimand, the population, primary variable and summary measure will be the same as the primary estimand, but the intercurrent event of corticosteroid dose increase and/or intravenous administration of corticosteroid will be ignored following a treatment policy strategy. The supplementary estimand will capture the effect of canakinumab regardless of increase in systemic corticosteroid dose and intravenous administration of steroid, reflecting possibly the situation under clinical practice.

The primary analysis will be repeated for the supplementary estimand without handling of systemic corticosteroid dose increase and/or iv corticosteroid use before Week 8 for any reason described in Section 2.5.3., i.e. even when a participant had these events, adapted ACR 30 assessment at Week 8 will be included as observed. Hypothesis testing will not be performed.

2.5.6 Supportive analyses

The primary analysis will be repeated, using data from all 14 participants, based on the FAS at the timing of the Week 28 interim analysis. Hypothesis testing will not be performed.

2.6 Analysis of the key secondary objective

2.6.1 Key secondary endpoint

The secondary clinical question of interest is: What is the effect of Canakinumab on oral corticosteroids tapering in Japanese AOSD participants after Week 8 up to Week 28?

The justification for the secondary estimand is that it will capture the ability of canakinumab on corticosteroid tapering based on the success criteria starting from Week 8 up to Week 28 after canakinumab administration.

The secondary estimand is described by the following attributes:

1. Population: Japanese AOSD participants who use systemic corticosteroid at baseline and are administered canakinumab at Week 8.

2. Endpoint: Successful oral corticosteroids tapering by Week 28. Participants will be considered as being able to taper oral corticosteroid according to pre-defined criteria depending on baseline dose.
3. Treatment of interest: canakinumab 4mg/kg.

The analysis will account for different intercurrent events as explained in the following:

1. Discontinuation of study treatment after Week 8 for any reason: If a participant early discontinued study treatment after Week 8 but had the Week 28 assessment regarding corticosteroid tapering, he/she will be included in the analysis.
2. Intravenous administration of steroid at any time between Week 8 and Week 28: If a participant had intravenous administration of steroid at any time between Week 8 and Week 28 assessment visit (i.e. between Week 8 visit and Week 28 visit), he/she will be considered as corticosteroid tapering failure at Week 28 regardless of whether the corticosteroid data is available (non-responder imputation)

The summary measure: proportion of participants who are able to taper oral corticosteroids successfully at Week 28.

2.6.2 Statistical hypothesis, model, and method of analysis

Frequency table with the number and percentage of participants who were able to taper oral corticosteroids successfully at Week 28 will be provided for the participants in the FAS who used systemic corticosteroid at baseline and were administered study treatment at Week 8, i.e. the number of evaluable participants could be smaller than the number of participants in the FAS. Participants who were able to taper oral corticosteroids successfully at Week 28 will be classified as “Tapered” or “Steroid free”, and “Steroid free” is defined as participants that did not use the steroid in the last point of time.

This analysis will also be performed by the subgroups described in Section 2.2.1.

2.6.3 Handling of missing values/censoring/discontinuations

If the successful tapering of corticosteroids can not be derived due to missing information, it will be imputed with the last available data from Week 8 to Week 28 (last observation carried forward (LOCF) approach).

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

The secondary efficacy endpoints of this study are Adapted ACR 30/50/70/90/100 response criteria, components of adapted ACR criteria, corticosteroid dose tapering, rash, DAS28-CRP, systemic feature score, and total IL-1β level.

2.7.2 Statistical hypothesis, model, and method of analysis

All efficacy endpoints will be summarized using the FAS. All analyses for secondary endpoints will be basically performed using data from all 14 participants based on the FAS. The analyses that will be performed based on the data up to the time when the first 11 participants in the FAS is described in Section 2.14.

Adapted ACR 30/50/70/90/100 response criteria

The adapted ACR 30/50/70/90/100 at Week 8 and the adapted ACR 30/50/70/90/100 at each visit including Week 8 will be analyzed separately.

For the adapted ACR 50/70/90/100 at Week 8, the primary analysis will be repeated as performed for adapted ACR 30 except the statistical hypothesis testing. The results will be presented with the primary analysis of the adapted ACR 30. In addition, the adapted ACR 30/50/70/90/100 response at Week 8 will be summarized with the number and percentage of participants by the subgroups described in Section 2.2.1.

For the adapted ACR 30/50/70/90/100 at each visit, frequency tables with the number and percentage of participants achieving the adapted ACR 30/50/70/90/100 criteria will be provided by scheduled visit.

The line plot of the percentage of participants achieving the adapted ACR 30/50/70/90/100 response for each visit will be provided.

Components of adapted ACR criteria

For the adapted ACR individual components from 1 to 5, summary statistics for the observed values and the change/percent change from baseline will be provided by scheduled visit. For absence of intermittent fever in the preceding week, frequency tables with the number and percentage of participants with or without intermittent fever will be provided by scheduled visit.

The 6 adapted ACR individual components are defined as follows:

1. Physician’s global assessment of disease activity
2. Participant's assessment of disease activity (Participant’s overall well-being)
3. Functional ability assessed using Health Assessment Questionnaire (HAQ)
4. Number of active joints (68 joints evaluated for pain/tenderness and 66 for swelling)
5. Laboratory measure of inflammation: CRP (standardized) (mg/L)
6. Absence of intermittent fever in the preceding week

Corticosteroid dose tapering

For oral corticosteroid dose, summary statistics for the change/percent change from baseline will be provided by scheduled visit after Week 8. The scheduled visits are defined as every 4 weeks through Week 48 and every 12 weeks thereafter.

The oral corticosteroid dose will be derived on prednisone equivalent dose per day (mg/day).

Rash

Frequency table with the number and percentage of participants in absent/present and typical or/and atypical if present will be provided by scheduled visit.

DAS28-CRP

Summary statistics for the observed values and the change/percent change from baseline will be provided by scheduled visit.

Frequency table with the number and percentage of participants in each category of DAS28-CRP (high disease activity, moderate disease activity, low disease activity, and remission) will be provided by scheduled visit.

Frequency table with the number and percentage of participants in each category of EULAR response criteria (based on DAS28-CRP) (good response, moderate response, and no response) will be provided by scheduled visit.

Details on how to categorize the DAS28-CRP and EULAR response criteria are given in Section 5.6.2.

Systemic feature score

For total score, summary statistics for the observed values and the change/percent change from baseline will be provided by scheduled visit.

For each component score, the number and percentage of participants whose score is 1 (present) will be provided by scheduled visit.

The total score will be calculated by summing the scores of each component and is defined as an integer value 0 to 10. The total score will be calculated only when all components are available.

Each component will be assigned a score of 1 (present) or 0 (absent) as follows:

- Fever [defined as a body temperature >37.5°C at least once a day during at least 5 consecutive days]
- Rash [defined by the presence of typical salmon-pink rash on the trunk and elsewhere during the febrile episodes]
- Serositis
- Lymphadenopathy [defined by lymph node enlargement to >1.5 cm localized anywhere within the body]
- Hepatomegaly and/or splenomegaly that had been confirmed by ultrasound evaluation

At baseline, laboratory features were considered present based on the following:

- ESR ≥20 mm/hour
- CRP (observed) ≥10 mg/liter
- White blood cell (WBC) count ≥12 x 10^9/liter
- Hemoglobin ≤11 g/dl
- Platelet count ≥400 x 10^9/liter.

During treatment epochs and at follow up visits, the laboratory parameters were scored as follows:

- ESR, score of 0 if <20 mm/hour or if decreased by ≥30% compared to baseline, score of 1 if increased or if decreased by <30% compared to baseline
- CRP, score of 0 if <10 mg/liter or if decreased by ≥30% compared to baseline, score of 1 if increased or if decreased by <30%
- WBC count, score of 0 if <12 x 10^9/liter or if decreased by ≥20% compared to baseline, score of 1 if increased or if decreased by <20%
- Hemoglobin level, score of 0 if >11 g/dl or if increased by ≥20% compared to baseline, but score of 1 if decreased or if increased by <20%;
- Platelet count, score of 0 if <400 x 10^9/liter or if decreased by ≥20% compared to baseline, score of 1 if increased or if decreased by <20%.

2.7.3 Handling of missing values/censoring/discontinuations

For the adapted ACR 50/70/90/100 at Week 8, the same handling of intercurrent events and missing values will be applied as for the adapted ACR 30.

For other endpoints, imputation of missing values will not be performed, and all endpoints will be tabulated based on observed data.

2.8 Safety analyses

For all safety analyses, the Safety set will be used. The summary tables by visit will include the assessments at the scheduled visits unless otherwise specified. All listings will include unscheduled visits.

At the interim analyses, as described in Section 2.1, all available data at the cut-off date will be included for safety analyses.

For the Week 28 IA, AEs will be summarized up to Week 28 and entire treatment period. Exposure adjusted event rate will be provided for entire treatment period. For laboratory, ECG and vital signs, by-visit summaries will be provided up to Week 28. Incidence rates of notable abnormalities will be provided for the period up to Week 28 and entire treatment period.

For the Week 48 IA, AEs will be summarized up to Week 48 and entire treatment period. Exposure adjusted event rate will be provided for entire treatment period. For laboratory, ECG and vital signs, by-visit summaries will be provided up to Week 48. Incidence rates of notable abnormalities will be provided for the period up to Week 48 and entire treatment period.

For the final analysis, all safety data will be summarized for entire treatment period.

2.8.1 Adverse events (AEs)

AEs will be coded using the MedDRA dictionary that provides the primary system organ class (SOC) and preferred term (PT) information.

All information obtained on AEs will be displayed by participant. A listing will include all AEs collected on eCRF during the study from screening period and treatment period.

Treatment emergent AEs (events started after the first dose of study medication or events present prior to start of study treatment but increased in severity based on preferred term) will be summarized by presenting, the number and percentage of participants having any AE, having any AE in each primary SOC, and having each individual AE based on the PT. A participant with multiple AEs within a primary SOC is only counted once towards the total of the primary SOC.

The following summary tables will be provided.

- All treatment emergent AEs regardless of study drug relationship by SOC and PT
- All treatment emergent AEs regardless of study drug relationship by maximum severity, SOC and PT
- All treatment emergent AEs regardless of study drug relationship, leading to study drug discontinuation, by SOC and PT
- All treatment emergent AEs regardless of study drug relationship, requiring concomitant medication or non-drug therapy, by SOC and PT
- Treatment emergent serious AEs regardless of study drug relationship by SOC and PT
- Treatment emergent AEs related to study drug treatment by SOC and PT
- Treatment emergent serious AEs related to study drug treatment by SOC and PT
- A summary of death, serious AEs, AEs related to study drug treatment, AEs leading to study drug discontinuation

Exposure adjusted event rate (per 100 participant-years) of treatment emergent AEs will be summarized by SOC and PT. The event rate (ER) per 100 participant-years will be calculated as follows:

ER = 100 * total number of occurrence of events / total participant-years,

where total participant-years is the sum of all participants' exposure times, i.e. duration of exposure from the day of the first dose of study treatment to the day of the last study visit.

To support the registration dossier, treatment emergent AEs will also be summarized by SOC, PT and onset period at the 28 Week IA and the 48 week IA using the data up to Week 28 and Week 48, respectively. Deaths, SAEs other than deaths, and AEs causing study treatment discontinuation will also be summarized. The following intervals will be used:

- 0-<4 weeks (1-<28 days)
- ≥4-<12 weeks (≥28-<84 days)
- ≥12-<24 weeks (≥84-<168 days)
- ≥24-<36 weeks (≥168-<252 days)
- ≥36-<48 weeks (≥252-<336 days)
- ≥48 weeks (≥336 days).

Note: at the Week 28 IA, the intervals after 24 weeks will be combined, i.e., ≥24 weeks (≥168 days).

Treatment emergent AEs will be summarized by SOC and PT and by the subgroups described in Section 2.2.1 at the 28 Week IA and the 48 Week IA using the all available data at the time point for the analysis.

Serious adverse events, adverse events leading to study drug discontinuation, adverse events requiring interruption, and adverse events requiring concomitant medication or non-drug therapy will be listed if any.

2.8.1.1 Adverse events of special interest / grouping of AEs

Adverse events of special interest (AESI) (e.g., potential and identified risks) will be defined based on the latest Case Retrieval Strategy (eCRS). Besides the risks defined on the eCRS, the J-RMP potential risk: anaphylactic reaction (SMQ) narrow will also be summarized. The comprehensive search of AESI will be performed for all treatment emergent AEs. Regarding the definition of Canakinumab - immunosuppressants combination therapy toxicity, the newly occurring serious infections which are defined in the eCRS (i.e., "infections – all indications" and "opportunistic infections - IHD indications") during combination therapy with Canakinumab plus immunosuppressants which are defined in the eCRS (i.e., Anatomical Therapeutic Chemical (ATC) classification drug codes L04AA: selective immunosuppressants, L04AX: other immunosuppressants, L04AB: tumor necrosis factor alpha (TNF-Alpha) inhibitors) will be identified to be summarized.

The number and percentage of participants with AEs of special interest will be summarized.

A listing of the definition of AESI in the eCRS will be provided.

The following safety topics of interest will be identified:

- Neutropenia (all indications)
- Interactions with vaccines (all indications)
- Canakinumab - immunosuppressants combination therapy toxicity (for CAPS PFS and Still's disease)
- Infections (all indications)
- Drug Induced Liver Injury (DILI hepatic transaminase and bilirubin elevations) (Still's disease)
- Opportunistic infections - IHD indications
- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Malignancy (all indications)
- Macrophage activation syndrome (Still's disease)
- Anaphylactic reaction (SMQ) narrow

The search terms will be based on the latest eCRS (i.e., version 26.0 as of 2-Oct-2023) and the safety topics of interest will be reviewed at each analysis.

2.8.1.2 Requirements of ClinicalTrials.gov and EudraCT

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events 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.

If for a same participant, 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 of study treatment relationship will be provided by SOC and PT.

These tables will be provided at the final analysis.

2.8.2 Deaths

Death, if any, will be listed.

2.8.3 Laboratory data

Laboratory parameters will be summarized by presenting descriptive statistics for hematology and biochemistry. The absolute values and change from baseline will be summarized by scheduled visit presenting mean, standard deviation, median, minimum, maximum and number of participants with non-missing data. Change from baseline will be summarized for participants with both baseline and post baseline values.

Shift tables of baseline to the worst post baseline value and to the last post baseline value based on normal ranges will be provided for hematology and biochemistry if normal ranges are available. The measurements on the unscheduled visits will be taken into account for the shift tables.

Incidence rates of notable abnormalities newly occurred after baseline (see Section 5.4) at any visit (including the unscheduled visits) will be presented. The denominator will be the number of participants at risk (i.e., the number of participants having a baseline measurement not meeting the criteria or missing but having at least one post-baseline measurement).

A listing for participants satisfying at least one criterion for notable abnormalities newly after baseline will be listed by participant and visit. A listing for all parameters with High or/and Low values based on normal range or with abnormality detected will be listed by participant and visit and if normal ranges are available abnormal values will be flagged. However, for the listing of participants with newly occurring liver enzyme abnormalities, all parameters will be listed.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

ECG measurements will be summarized by presenting descriptive statistics for the absolute values and changes from baseline by scheduled visit. Change from baseline will be summarized for participants with both baseline and post baseline values.

All information collected will be listed by participant and visit.

2.8.4.2 Vital signs

Vital signs will be summarized by presenting descriptive statistics for the absolute values and changes from baseline by scheduled visit. Change from baseline will be summarized for participants with both baseline and post baseline values.

Incidence rates of notable abnormalities newly occurred after baseline (see Section 5.4) at any visit (including the unscheduled visits) will be presented. A listing for participants satisfying at least one criterion for notable abnormalities newly after baseline will be listed by participant and visit.

2.8.4.3 Immunogenicity

All immunogenicity results will be listed by participant and visit.

2.8.4.4 Adjudication committee data

MAS adjudication committee is planned. The data reported by the adjudication committee will be listed if any.

2.9 Pharmacokinetic endpoints

Pharmacokinetic parameters will be listed by participant and visit. Descriptive summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum for the FAS.

2.10 PD and PK/PD analyses

PD parameter (Total IL-1β) will be summarized by means of arithmetic and geometric mean, SD, CV for arithmetic and geometric mean, median, minimum and maximum for the FAS.

2.11 CCI

CCI

2.12 CCI

CCI

2.13 CCI

CCI

2.14 Interim analysis

Two interim analyses will be performed after all participants have completed Week 28 to support the registration dossier, and Week 48 to supplement the dossier with long-term safety and efficacy data. At the interim analysis at Week 28, the primary efficacy analysis will be conducted based on the data up to the time when the first 11 participants have reached Week 28 (or prematurely discontinued prior to Week 28), that is 6Dec2022, CCI .

For the primary efficacy analysis with the first 11 participants, only the endpoints presented below will be analyzed.

- Participant demographics
- Baseline participant characteristics
- Adapted ACR 30/50/70/90/100 response at Week 8 (primary estimand)
- Subgroup analyses based on prior use of Tocilizumab
- Adapted ACR 30/50/70/90/100 response by visit

- Line plot of adapted ACR 30/50/70/90/100
- Successful oral corticosteroid tapering at Week 28
- Successful oral corticosteroid tapering by visit after Week 8
- Prednisone equivalent dose tapered to below 5 mg/day
- Oral corticosteroid dose (mg/day) by visit
- Each component of adapted ACR criteria by visit
- Rash by visit
- DAS28-CRP by visit
- DAS28-CRP response by visit
- EULAR response by visit
- Systemic feature score: Total score by visit
- Systemic feature score: Each component score by visit
- Ferritin level by visit
- Spaghetti plot of ferritin level by visit
- Number of tender/swollen joints
- Standardized CRP within normal range

The analysis set to be used in the analysis presented above will include up to about 11 participants.

After all participants have completed Week 28 and Week 48, two interim analyses will be performed on the efficacy and safety data during the study:

One will be at Week 28, to support the registration dossier and the other will be at Week 48 to supplement the dossier with long-term safety and efficacy data.

At the interim analyses, the data cut-off date for Week 28/Week 48 analysis will be the date of Week 28/Week 48 visit for the last participant. For efficacy analyses including PK/PD and biomarker-related analyses, the data up to Week 28/Week 48 visit for each individual participant will be included. For safety analyses and summaries for treatments, all available data will be included.

At the interim analyses, for participants who discontinued before Week 28/Week 48 visit, the data up to the time of discontinuation will be included for efficacy and safety analyses. For participants who discontinued after Week 28/Week 48 visit, all available data up to the time of discontinuation will be included for safety analyses, but the data up to Week 28/Week 48 will be included for efficacy analyses. For participants who early discontinued, the EOS visit will be remapped using the pre-defined time window before the data cut-off. When the data up to the specific timepoints cannot be extracted, all data available at data base lock will be reported.

3 Sample size calculation

CCI

4 Change to protocol specified analyses

NA

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

No imputation will be made to the start and end date of study treatment.

5.1.2 AE date imputation

No imputation will be made to the start and end date of AE.

5.1.3 Concomitant medication date imputation

5.1.3.1 CM start date imputation

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

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) Uncertain	(1) Uncertain	(1) Uncertain	(1) Uncertain
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.a) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

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 start 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 start 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 start 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 to treatment start date.

   b. Else if the CM month is less than the treatment start 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 start 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.

5.1.3.2 CM end date imputation

1. If the CM end date month is missing, the imputed end date should be set to the earliest of the (31DECYYYY, date of death).
2. If the CM end date day is missing, the imputed end date should be set to the earliest of the (last day of the month, date of death).
3. If CM end date year is missing or CM is ongoing, the end date will not be imputed.
4. If the imputed CM end date is less than the existing CM start date then use CM start date as CM end date.

5.1.3.3 Prior therapies date imputation

No imputation will be made to the start and end date of prior therapy.

5.1.3.4 Post therapies date imputation

No imputation will be made to the start and end date of post therapy.

5.1.3.5 Other imputations

Start data of medical history

Partial dates are allowed for the start date of the medical history. If the day is missing, 15th will be imputed. If the month and day are missing, July 1st will be imputed. If the year is missing, it will be treated as a missing value.

5.2 AEs coding/grading

AEs are coded using the MedDRA terminology.

5.3 Laboratory parameters derivations

NA

5.4 Clinically notable laboratory values and vital signs

The following defined notable laboratory or vital sign abnormalities will be used.

Newly occurring selected notable laboratory abnormalities :

- Albumin: < LLN
- >3x-, 5x-, 8x-, 10x-, and 20x-ULN elevations of AST, ALT, and either ALT or AST*
- Any elevations of bilirubin > ULN; elevated bilirubin to >1.5xULN, and to >2xULN*
- Any elevations of ALP >1.5xULN, >2xULN, >3xULN, >5xULN *
- Elevation of AST and/or ALT (>3xULN, >5x-, >10x) accompanied by elevated bilirubin (>2xULN)*
- ALT or AST >3x ULN and TBL >2x-, and ALP <2xULN
- ALP >3x-, 5x ULN and TBL >2xULN
- Gamma-Glutamyl transferase (GGT): > ULN, 3 x ULN, 5 x ULN
- Creatinine (serum): ≥ 1.5 x ULN
- Creatinine clearance (Cockroft-Gault formula‡):
  - ≥ 25% decrease from baseline†
  - ≥ 25% decrease from baseline† and ≥3 months in duration§
  - ≥ 25% decrease from baseline† in combination with protein urine dipstick resulting in new protein ≥1+ and ≥3 months in duration§
- Potassium: ≥ 5.5 mmol/L, or ≤ 3.0 mmol/L
- Magnesium: ≥ 1.5 mmol/L, or ≤ 0.5 mmol/L
- Sodium: ≥ 150 mmol/L, or ≤ 130 mmol/L
- Calcium: ≥ 1.2 x ULN or < LLN

- Hemoglobin: ≥2 g/dL decrease from baseline, or < 10.0 g/dL
- Criteria based on CTC grades for hemoglobin: Grade 1 (<LLN – 100 g/L), Grade 2 (<100 – 80 g/L), Grade 3 (<80 – 65 g/L), Grade 4 (<65 g/L)
- Platelet count: < LLN
- Criteria based on CTC grades for platelet: Grade 1 (<LLN – 75.0 x 10E9/L), Grade 2 (<75.0 – 50.0 x 10E9/L), Grade 3 (<50.0 – 25.0 x 10E9/L), Grade 4 (<25.0 x 10E9/L)
- White blood cell count: ≤ 0.8 x LLN or ≥ 1.2 x ULN
- Criteria based on CTC grades for white blood cell count: Grade 1 (<LLN – 3.0 x10E9/L), Grade 2 (<3.0 – 2.0 x10E9/L), Grade 3 (<2.0 – 1.0 x10E9/L), Grade 4 (<1.0 x10E9/L)
- Absolute Neutrophils: ≤0.9 x LLN or ≥ 1.2 x ULN
- Criteria based on CTC grades for absolute neutrophils: Grade 1 (<LLN – 1.5 x 10E9/L), Grade 2 (<1.5 – 1.0 x 10E9/L), Grade 3 (<1.0 – 0.5 x 10E9/L), Grade 4 (<0.5 x 10E9/L)
- Absolute Eosinophils: ≥ 1.1 x ULN, ≥ 0.45 x 10E9/L
- Absolute Lymphocytes: < LLN or ≥ 1.1 x ULN
- Protein urine dipstick: ≥ ++, New protein ≥1+, ≥3 months in duration
- Total Cholesterol: ≥1.5 x ULN
- Triglycerides: ≥5.7 mmol/L

† Baseline is defined as the mean in two consecutive visits that are ≥ 14 days apart. If there are not two consecutive visits that are ≥ 14 days apart, baseline values will be used.

§ The notable laboratory abnormalities will be assessed for each assessment and presented in the table. The duration will be picked up manually.

‡ Cockroft-Gault formula is defined by sex as follows:

Cockroft-Gault formula (Men): CrCl (mL/min) = [((140-age (years)) x weight (kg)) / (serum creatinine(μmol/L) / 88.4) (mg/dL) x 72] ,

Cockroft-Gault formula (Women): CrCl (mL/min) = [((140-age (years)) x weight (kg)) / (serumcreatinine (μmol/L) / 88.4) (mg/dL) x 72] x 0.85.

Newly occurring selected notable vital signs abnormalities :

- Systolic blood pressure: ≥25% decrease or ≥25% increase from baseline.
- Diastolic blood pressure: ≥25% decrease or ≥25% increase from baseline.
- Systolic blood pressure and Diastolic blood pressure: increase to ≥140 and 90, respectively.
- Pulse: ≥110 bpm with ≥15% change from baseline, or < 50 bpm with ≥15% change from baseline

* FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation

Note: Only post-baseline values will be flagged as notable abnormalities

5.5 Statistical models

Primary analysis

No statistical model will be used for the primary analysis.

Key secondary analysis

No statistical model will be used for the key secondary analysis.

Rule of exclusion criteria of analysis sets

The protocol deviations that cause participants to be excluded from the analyses are listed in Table 5-1.

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

Deviation ID	Description of Deviation	Exclusion in Analyses
INCL01	No signed informed consent was obtained before any assessments were performed	Excluded from both FAS and Safety set
TRT02	Participant was not exposed to study medication at any visit	Excluded from both FAS and Safety set

5.6 Documentation of statistical methods

5.6.1 Calculation of prednisone equivalent dose (mg/kg/day) of oral steroids

The oral steroid dose at baseline will be the measurement on the date of baseline (Day 1) recorded on the concomitant medication page in eCRF. The oral steroid used for AOSD indication will be used. The oral steroid dose will be converted to prednisone equivalent dose using the conversion factor in Table 5-2. The prednisolone equivalent dose will be derived by dividing the dose of the oral steroid dose by the corresponding conversion factor. Body weight will be the measurement at baseline (Day 1) or the last available weight before baseline.

The oral steroid dose at post-baseline assessment visits after Week 8 will be the measurement on one day before the date of corresponding assessment visits. Body weight will be the last available measurement on or before the date of steroid dose measurement.

The daily dose will be calculated by multiplying the conversion factors corresponding to the frequency recorded in eCRF (see Table 5-3). If participants use more than 2 oral steroids for AOSD on the same day, total dose per day will be used.

When a participant continued the study, if there is no concomitant oral steroid data at the assessment day, it will be considered as steroid free (0 mg).

If the oral steroid data is available but with missing information (e.g., body weight, frequency), the prednisone equivalent dose will be set to missing.

For example, if a participant weighs *w* kg and is taking *x* mg of Betamethasone 2 times per day and *y* mg of Hydrocortisone 3 times per day, the prednisone equivalent dose will be calculated as follows:

Prednisone equivalent dose per day = (x/0.12*2 + y/4*3)/w.

Table 5-2 Conversion factors for steroid medications

Medication	Conversion factor
Betamethasone	0.12
Hydrocortisone	4
Cortisone	5
Deflazacort	1.2
Dexamethasone	0.15
Methylprednisolone	0.8
Prednisolone	1
Triamcinolone	0.8
Prednisone	1

Table 5-3 Conversion factors for frequencies

Frequency	Conversion factor
2 Times per day	2
Every month	1/28
As needed	1
Every 24 hours	1
Every other day	1/2
3 Times per day	3
4 Times per day	4
Once	1
Daily	1
Every week	1/7
2 Times per week	2/7
3 Times per week	3/7
4 Times per week	4/7
Per annum	1/365.25
Every 4 hours	6
Every 6 hours	4
Every 8 hours	3
Unknown	Missing
Other	Missing

5.6.2 DAS28-CRP

The Disease Activity Score (DAS28) (Prevoo et al 1995; Fransen et al 2003) is a combined index to measure the disease activity in patients with Rheumatoid arthritis.

Calculation of DAS28-CRP

The following formula to calculate the DAS28 using standardized CRP (mg/L) will be used:

DAS28-CRP = 0.56*sqrt(28 Tender joint count) + 0.28*sqrt(28 Swollen joint count) + 0.36 * ln(standardized CRP in mg/L + 1) + 0.014*Participant's assessment of disease activity (Participant's overall well-being) (0-100mm) + 0.96

The score will be calculated only when all components are available. If any component measurement is missing, DAS28-CRP will be missing. The following 28 joints will be assessed for tenderness and swelling: metacarpophalangeal I-V(10), thumb interphalangeal (2), hand proximal interphalangeal II-V (8), wrist (2), elbow(2), shoulders (2), and knees (2).

Categorization of DAS28-CRP

High disease activity:	DAS28 at the timepoint > 5.1
Moderate disease activity:	3.2 ≤ DAS28 at the timepoint ≤ 5.1
Low disease activity:	2.6 ≤ DAS28 at the timepoint < 3.2
Remission:	DAS28 at the timepoint < 2.6

EULAR response criteria (based on DAS28-CRP)

Good response:	ΔDAS28 > 1.2 and DAS28 at the timepoint ≤ 3.2
Moderate response:	ΔDAS28 > 1.2 and DAS28 at the timepoint > 3.2
	or 0.6 < ΔDAS28 ≤1.2 and DAS28 at the timepoint ≤5.1
No response:	ΔDAS28 ≤ 0.6
	or 0.6 < ΔDAS28 ≤ 1.2 and DAS28 at the timepoint > 5.1

where ΔDAS28 is the improvement in DAS28 from baseline.

6 Reference

Fransen J, Welsing PMJ, de Keijzer RMH, et al (2003) Development and validation of the DAS28 using CRP. Ann Rheum Dis; 62(Suppl 1):10.

Prevoo ML, van 't Hof MA, Kuper HH, et al (1995) Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum; 38(1):44-8.