NOVARTIS

Clinical Development

Canakinumab / ACZ885

ACZ885N2301 / NCT02059291

A randomized, double-blind, placebo controlled study of canakinumab in patients with Hereditary Periodic Fevers (TRAPS, HIDS, or crFMF), with subsequent randomized withdrawal/ dosing frequency reduction and open-label long term treatment epochs

Statistical Analysis Plan

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Version	Date	Changes
Amendment 1.0	12.12.2014	Incorporate changes from protocol amendment 1: adding analysis statement for patients >28 days but <2 years old who enter the study directly into the open-label arm of Epoch 2; Update Notable Blood pressure normal range to include patients less than 2 years old. Adding Sensitivity analyses section.
Amendment 2.0	09.10.2015	Additional analysis added for primary and secondary endpoints. Shift analysis for CKD categories added.
Amendment 3.0	24.10.2015	Imputation rule for missing standardized local CRP value is added. Detailed definition of duration of exposure added. Detailed summary around CRP categories before day 29 added. Details around rescue medication analysis added.
Addendum	01.12.2015	Updated to include AEs and concomitant medications occurred during safety follow period after epoch 2 in listings and add two additional sensitivity analysis
Addendum 2	07.01.2015	Adding time to first resolution of fever analysis; Adding plot analysis; Adding gene analyses.
Amendment 1.0 Epoch 3	26.02.2016	Updated definition of safety set Epoch 3 Treatment label update for epoch 3 Added method to calculate cumulative dose in epoch 3 and 4 AIDAI weekly scores changed to AIDAI monthly scores
Addendum 1.0 Epoch 3	26.04.2016	Clarification on derivation of AIDAI monthly score is added.
Final analysis	10.01.2017	Added dose distribution over time from epoch 2 to epoch 4, summary tables of CRP, SAA, PGA starting from epoch 2 to epoch 4. AE/SAE combing epoch 2 to epoch 4 data after patients taking ACZ885. Additional two safety summary tables are added for Health Authority data disclosure requirements (EudraCT and CT.gov).

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List of abbreviations

AE	Adverse Event
AIDAI	Auto-Inflammatory Disease Activity Index
ALT	Alanine Aminotransferase (SGPT)
AST	Aspartate Aminotransferase (SGOT)
BMI	Body Mass Index
CHQ-PF50	Child Health Questionnaire
CRP	C-reactive Protein
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic case report/record form
FAS	Full Analysis Set
crFMF	colchicine resistant Familial Mediterranean Fever
HIDS	Hyper IgD Syndrome
IL-1β	Interleukin-1β
LLN	Lower Limit of Normal
MedDRA	Medical dictionary for regulatory activities
PD	Pharmacodynamic(s)
PGA	Physician's global assessment
PhS	CHQ-PF50 physical component summary measure
PK	Pharmacokinetic(s)
PPGA	Patient/ Parent's global assessment
PsS	CHQ-PF50 psychosocial component summary measure
SAA	Serum Amyloid A
SAE	Serious Adverse Event
s.c.	subcutaneous(ly)
SDS	Sheehan Disability Scale
SF-12	Short Form (12) Health Survey
SGOT	Serum Glutamic Oxaloacetic Transaminase, same as AST
SGPT	Serum Glutamic Pyruvic Transaminase, same as ALT
TBL	Total Bilirubin
TRAPS	TNF-receptor Associated Periodic Syndrome

ULN	Upper Normal Limit
VAS	Visual Analog Scale

1 Statistical methods planned in the protocol and determination of sample size

Data will be analyzed by Quanticate according to the data analysis section 9 of the study protocol which is available in Appendix 16.1.1 of the Clinical Study Report (CSR). Important information is given in the following sections and details will be provided, as applicable, in Appendix 16.1.9 of the CSR.

1.1 Statistical and analytical plans

The planned analysis is described in Section 9 (Data Analysis) of the study protocol which is available in Appendix 16.1.1 of the CSR.

This document covers statistical and analytical plans for the primary endpoint analysis i.e. the resolution of the index flare at the time of randomization and the absence of incident flares over the first 16 weeks after randomization, at Week 16 interim analysis but also covers the analyses for the Week 40 interim analysis and the final analysis after database lock. The data collected in this study up to the time of the Week 16 interim analysis will be part of the marketing authorization submission package of the ACZ885N project. All data collected up to Week 16 will be analyzed in the Week 16 interim analysis.

This study consists of 3 cohorts (one cohort per condition: TNF-receptor Associated Periodic Syndrome (TRAPS), Hyper IgD Syndrome (HIDS) and colchicine resistant Familial Mediterranean Fever (crFMF)), and 4 study epochs.

Each cohort will follow the same study design across the 4 epochs:

- A screening epoch to assess patients' eligibility of up to 12 weeks duration (Epoch 1)
- A randomized treatment epoch (Epoch 2) of 16 weeks which will provide efficacy and safety data in a double-blind placebo-controlled parallel-arm setting. This randomized treatment epoch will include 2 possible escape options: Blinded escape (from Day 8 to Day 28), Open-label treatment (from Day 29 to Day 112)
- A randomized withdrawal epoch (Epoch 3) of 24 weeks where Canakinumab responder patients will be re-randomized to canakinumab 150 mg q8w or Placebo
- An open-label treatment epoch (Epoch 4) of 72 weeks to collect long-term safety data for canakinumab.

In order to provide access to treatment, roll-over TRAPS patients previously participating in clinical study CACZ885D2203 and/or the subsequent Multiple Patient Program (MPP) treatment plan CACZ885D2207M will be allowed to enter the study in randomized withdrawal epoch (Epoch 3) and the Japanese crFMF patients with non-exon 10 mutations or patients >28 days but <2 years old (with bodyweight ≥3.75 kg) will enter the study in the open-label arm of randomized treatment epoch (Epoch 2). The non-randomized patient group including Japanese crFMF patients with non-exon 10 mutations and patients >28 days but <2 years old will follow the following study design across the 4 epochs:

a. A screening epoch to assess patients' eligibility of up to 12 weeks duration (Epoch 1)
b. An open-label epoch of 16 weeks (Epoch 2)
c. An open-label epoch of 24 weeks (Epoch 3)

d. An open-label treatment epoch of 72 weeks to collect long-term safety data for canakinumab (Epoch 4)

All data will be analyzed separately for each independent cohort (TRAPS, HIDS, crFMF).

The purpose of the study is to provide evidence supporting answers to following questions. The data will be analyzed by Epoch:

1. Whether canakinumab at a starting dose of 150mg s.c. (or 2mg/kg for patients ≤40 kg) administered every 4 weeks is able to induce and maintain a clinically me aningful reduction of disease activity defined as resolution of the index flare at Day 15 and no new disease flares over 16 weeks of treatment in a greater proportion of patients with TRAPS, HIDS, or crFMF compared to placebo (Data from Epoch 2)
2. Whether, in patients responding to the initial dosing regimen of every 4 weeks, canakinumab will maintain its clinical efficacy if administered at a reduced dosing interval of 150mg s.c. (or 2mg/kg for patients ≤40 kg) every 8 weeks. (Data from epoch 3 and 4)

Safety data for the subgroup of patients coming from ACZ885D2203 and/or the subsequent Multiple Patient Program (MPP) treatment plan CACZ885D2207M collected in Epoch 3 and 4 will separately be reported from the other patients who will be screened and randomized in Epoch 2.

Safety data for the subgroup of canakinumab naïve Japanese crFMF patients with non-exon 10 mutations, and patients >28 days but <2 years old, collected in Epoch 2, 3 and 4 will separately be reported from the other patients who will be screened and randomized in Epoch 2.

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum, and number of patients with non-missing data (n). Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies.

If not otherwise specified, p-values will be presented as two-sided p-values and two-sided confidence intervals will be displayed.

All listings will be presented by cohort and treatment sequence.

1.2 Subjects and treatments

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

The **Randomized Set** Epoch 2 will consist of all patients who are randomized in the randomized treatment epoch (Epoch 2).

The **Randomized Set** Epoch 3 will consist of all patients who received canakinumab drug in epoch 2 and are responders at week 16 and who are re-randomized in the randomized withdrawal epoch (Epoch 3).

Unless otherwise specified, mis-randomized patients (mis-randomized in IRT) will be excluded from the randomized set. (Mis-randomized patients are defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the patient's final randomization eligibility and no study medication was administered to the patient).

The **Full Analysis Set** (FAS) Epoch 2 will consist of all randomized patients in the randomized treatment epoch who received at least one dose of study drug in epoch 2. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

The **Full Analysis Set** (FAS) Epoch 3 will consist of all patients in the randomized withdrawal epoch who received at least one dose of study drug.

The **Safety Set** Epoch 2 will consist of all patients that received study treatment in Epoch 2. Patients will be analyzed according to treatment received. Of note, the statement that a subject had no AEs also constitutes a safety assessment.

The **Safety Set** Epoch 3 will consist of all patients that received study treatment in Epoch 3. Patients will be analyzed according to treatment received. Of note, the statement that a subject had no AEs also constitutes a safety assessment.

The **Safety Set** Epoch 4 will consist of all patients that received study treatment in Epoch 4. Patients will be analyzed according to treatment received. Of note, the statement that a subject had no AEs also constitutes a safety assessment.

The **Per-protocol Set (PPS)** Epoch 2 will consist of all patients in the FAS Epoch 2 who do not fulfill any criteria that could potentially confound the interpretation of analyses conducted on the FAS.

The protocol deviation (PD) population codes leading to exclusion from Per-protocol set are presented in Table 1-1. In addition, subjects receiving a single add-on injection before day 15 despite they don't fulfill criterion for add-on injection from Day 8 to Day 14 were excluded from Per-protocol set.

An analysis based on the per-protocol set will be performed as additional sensitivity analysis. Protocol deviations for exclusion from a per-protocol analysis are defined in Table 1-1.

Table 1-1 Subject classification rules

Analysis set	PD Categories Codes that cause subject to be excluded	Non-PD criteria that cause a subject to be excluded
Randomization set	INC01,INC02,INC20	Mis-randomized subject
FAS Epoch 2(Full Analysis Set)	INC01,INC02,INC20, TRT02	NA
FAS Epoch 3(Full Analysis Set)	INC01,INC02,INC20, TRT02	NA
Safety Epoch 2	INC02, TRT02	NA
Safety Epoch 3	INC02, TRT02	NA
Safety Epoch 4	INC02, TRT02	NA
Per-protocol Epoch 2	See notes*	1) subjects receiving a single add-on injection before day 15 despite they don't fulfill criterion for add-on injection from Day 8 to Day 14 2) subjects taking biologics after taking study medication and don't discontinue study drug

*the following are used to define Per-protocol analysis set:
Exclude the following
INCLXX: TRAPs (INC01,INCL02, INCL06, INCL07, INC20), HIDs(INC01, INCL02, INCL11, INCL12, INC20), crFMF(INC01, INCL02, INCL15, INCL18, INCL19, INC20)
TRTXX: TRT02, TRT07, TRT26

Definition of responders

Definition of responders in epoch 2: canakinumab treated patients in Epoch 2 who maintain a clinically meaningful response (absence of new flares) until week 16 from the time of the resolution of the index flare at day 15. All patients randomized to placebo at baseline and completing the randomized treatment epoch (Epoch 2) without any re-flare will be considered placebo-responders.

Definition of non-responders in epoch 2: In the randomized treatment epoch (Epoch 2), patients needing dose escalation in the canakinumab arms, or escape from Placebo arms to canakinumab, or discontinued from the study due to any reason prior to evaluating the primary endpoint at week 16 will be considered as non-responder in epoch 2.

Definition of responders in epoch 3: Responder in the Randomized withdrawal epoch (epoch 3) is defined as patients having no flare(s) between week 16 and week 40.

Definition of responders in epoch 4: Responders in the epoch 4 are defined as patients having no flare(s) between week 40 and end of the study.

1.3 Treatment group definitions

The following study epoch will be considered for analysis:

- **Epoch 2**: A randomized treatment epoch of 16 weeks. This randomized treatment epoch will include 2 possible escape options: Blinded escape, Open-label treatment
- **Epoch 3**: A randomized withdrawal epoch of 24 weeks

- **Epoch 4**: An open-label treatment epoch of 72 weeks.

Treatment groups for analysis will include:

Randomized treatment epoch (Epoch 2):

Treatment arms for the primary and secondary efficacy analyses will only include canakinumab 150 mg sc q4w and placebo.

Other efficacy and safety data will be displayed in Epoch 2 in the following way:

- Patients being randomized and not having a flare in epoch 2 (and not having received add-on dose or any up-titration)
- Patients being randomized and having at least one flare in epoch 2 and having been up-titrated only once (or received add-on dose) (150mg q4->300mg q4; Placebo->150mg q4)
- Patients being randomized and having at least one flare in epoch 2 and having been up-titrated at least twice (Placebo->300mg q4)

------- No flare--------- ---------- >= 1 Flare ----------

Randomized Open –label arm

150mg q4 Placebo 150mg q4->300mg q4 Pla->150mg q4 Pla->150mg q4->300mg q4

Randomized withdrawal epoch (Epoch 3):

As one of the objectives in epoch 3 is to look at the maintenance of efficacy, patients will be categorized in two groups: those being randomized and keeping their initial treatment arm until the end of epoch 3 (i.e. no having a flare) and the other patients where the cumulative dose (in mg) over the 24 weeks will be analyzed.

Safety and efficacy data will be displayed in Epoch 3 in the following way:

- Re-randomized & no up-titration ---- Cumulative dose in mg over 24 weeks ----

150mg q8 Placebo <600mg 600mg - <1200mg ≥1200mg

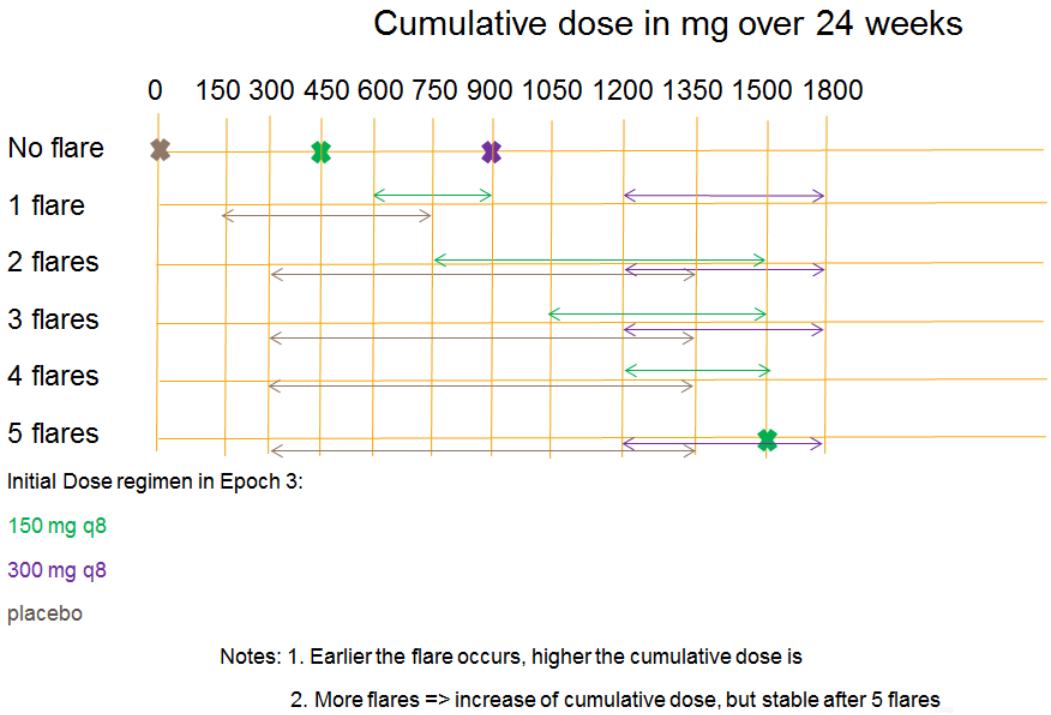
The cut-offs of 600mg, 1200mg were decided based on all options for cumulative dose over 24 weeks depending on the number of flares and initial dose regimen at start of epoch 3.

Example on how the cumulative dose is calculated over the 24 weeks:

Considering a patient taking initially 150 mg q8w at start of epoch 3 and having only one flare in epoch 3 then the patient will up titrate to 150 mg q4w. Here are the different cases. The first line shows the initial schedule with no flare. If no flare, the patient receives 3 injections of 150 mg each so a total of 450 mg over 24 weeks, from Day 113 to Day 281, with no dose at day 281(belongs to epoch 4).

	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253	Cumulative dose in mg
Dose: 150mg q8 with no flare	X 150mg		X 150mg		X 150mg		450mg
1 flare between D225-D253	X 150mg		X 150mg		X 150mg	X 150mg	600mg
1 flare between D197-D225	X 150mg		X 150mg		X 150mg	X 150mg	600mg
1 flare between D169-D197	X 150mg		X 150mg	X 150mg	X 150mg	X 150mg	750mg
1 flare between D141-D169	X 150mg		X 150mg	X 150mg	X 150mg	X 150mg	750mg
1 flare between D113-D141	X 150mg	X 150mg	X 150mg	X 150mg	X 150mg	X 150mg	900mg

Therefore for a patient taking initially 150mg q8w at the start of epoch 3 and having one flare in epoch 3, the range of cumulative dose over 24 weeks will be [600 mg-900 mg].



Notes: 1. Earlier the flare occurs, higher the cumulative dose is

2. More flares => increase of cumulative dose, but stable after 5 flares

Cumulative dose calculation for epoch 3:

For Patients weighing ≥7.5 kg and ≤40 kg, the dose is derived in mg/kg ie. Actual total dose (ml) x150mg / Weight(kg) at visit.

- If the sum of the dose (mg/kg) in Epoch 3 is ≤7mg/kg then the patient will be assigned to the dose level category <600mg.
- If the sum of the dose (mg/kg) in Epoch 3 is >7mg/kg -≤15mg/kg then the patient will be assigned to the dose level category ≥600mg-<1200mg.
- If the sum of the dose (mg/kg) in Epoch 3 is >15mg/kg then the patient will be assigned to the dose level category ≥1200mg.

For Patients weighing <7.5 kg, the dose is derived in mg/kg ie. Actual total dose (ml) x75mg / Weight(kg) at visit.

- If the sum of the dose (mg/kg) in Epoch 3 is ≤7mg/kg then the patient will be assigned to the dose level category <600mg.
- If the sum of the dose (mg/kg) in Epoch 3 is >7mg/kg -≤15mg/kg then the patient will be assigned to the dose level category ≥600mg-<1200mg.
- If the sum of the dose (mg/kg) in Epoch 3 is >15mg/kg then the patient will be assigned to the dose level category ≥1200mg.

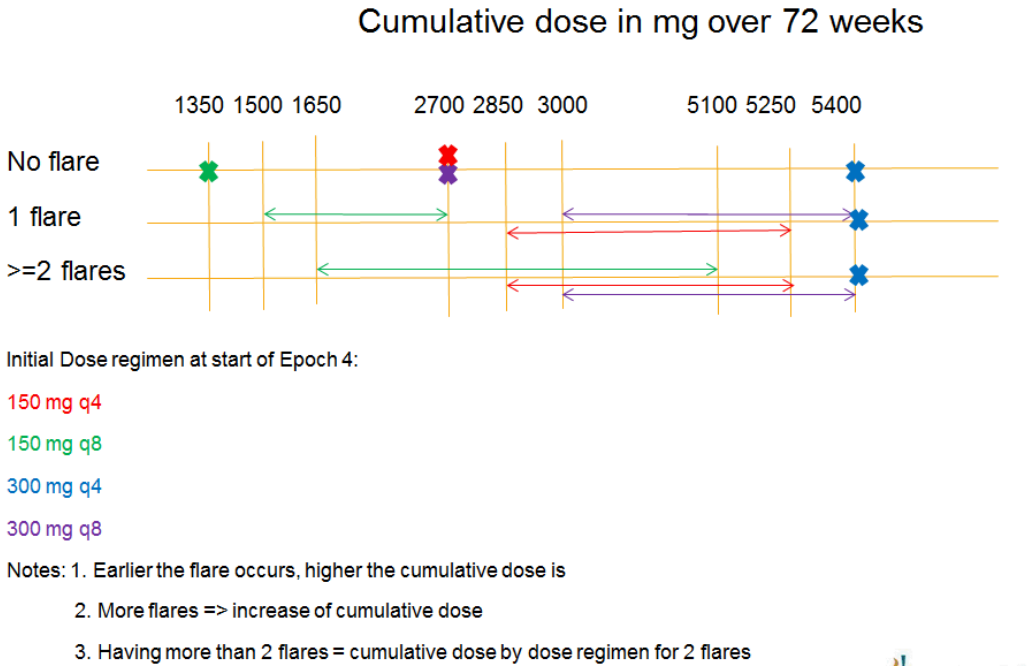
Open-label treatment epoch (Epoch 4):

As few patients are expected having no flare in epoch 4 for 72 weeks, then safety and efficacy data will be displayed using the cumulative dose over the 72 weeks in Epoch 4 in the following way:

----- Cumulative dose in mg over 72 weeks ----

<2700mg ≥2700mg- <5400mg ≥5400 mg

The cut-offs of 2700mg, and 5400mg were decided based on all options for cumulative dose over 72 weeks depending on the number of flares and initial dose regimen at start of epoch 4. The first group could be considered as patients taking initially 150mg q8w at start of epoch 4 with or without flare over 72 weeks, the second one grouping patients taking initially 150mg q4w or 300mg q8w at start of epoch 4 with or without flare over 72 weeks and the last one patients taking initially 300mg q4 with or without flare over 72 weeks.



Roll-over patients from ACZ885D2203/ CACZ885D2207M and naïve Japanese crFMF patients with non-exon 10 mutations and patients >28 days but <2 years old

Data for the subgroup of patients coming from ACZ885D2203 and/or the subsequent Multiple Patient Program (MPP) treatment plan CACZ885D2207M collected in Epoch 3 as well as canakinumab naïve Japanese crFMF patients with non-exon 10 mutations and patients >28 days but <2 years old collected in Epoch 2 and Epoch 3, will separately be reported from the other patients who will be screened and randomized in Epoch 2. For subgroup 1: Roll-over patients from ACZ885D2203/ CACZ885D2207M:

In epoch 3, for this subgroup of patients safety and efficacy data will be tabulated as follows:

---- Cumulative dose in mg over 24 weeks ----

<600mg 600mg - <1200mg ≥1200mg

In epoch 4, this subgroup of patients will be reported together with the other patients as follows:

----- Cumulative dose in mg over 72 weeks ----

<2700mg ≥2700mg- <5400mg ≥5400 mg

For subgroup 2: Naïve Japanese crFMF patients with non-exon 10 mutations and patients >28 days but <2 years old:

Patient Demographics & other baseline characteristics and Adverse events data for this subgroup will be tabulated under one treatment group ACZ885. All other safety and efficacy data will be listed under one treatment group ACZ885 in epoch 2 and epoch 3. This subgroup of patients will also be reported together with the other patients in epoch 4 using same cumulative dose categories.

1.4 Summary of the analyses

Table 1-2 Analysis by Epoch

Endpoint/analysis	Epoch			
	Epoch 2 (restricted to initial randomized treatment arms)	Epoch 2	Epoch 3	Epoch 4
Patient disposition	X	X	X	X
Demography & baseline characteristics	X	X	X	X
Medical history	X			
Previous & concomitant medication	X	X	X	X
Surgeries and medical procedures		X	X	X
Rescue medications	X	X	X	X
Study medication: duration of exposure	X	X	X	X
Proportion of responders at week 16	X			
Supportive analysis using SAA	X			
patients who achieve a PGA < 2 at Week 16	X			
Serologic remission at week 16	X			
Normalized SAA	X			
Responder in epoch 3 (only for canakinumab responder in epoch 2)			X	
CRP		X	X	X
PGA		X	X	X
PPGA		X	X	X
Physician's severity assessment of disease signs and symptoms over time		X	X	X
Fever		X	X	X
Blinded escape	X			
Time to new flare			X	
AIDAI	X	X	X	
SF-12	X	X	X	
CHQ-PF50	X	X	X	
SDS v3	X	X	X	
Total IL-1β		X	X	X
Adverse events		X	X	X
Laboratory data		X	X	X
Vital signs		X	X	X
ECG		X	X	X

1.5 Patient demographics and other baseline characteristics

Summary statistics will be provided for demographic and baseline characteristics for the below treatment groups, and by epoch:

1. In Epoch 2, by initial randomized treatment arms (canakinumab 150mg sc q4w, placebo, all subjects) and according to treatment groups defined in section 1.3
2. In Epoch 3, according to treatment groups defined in section 1.3
3. In Epoch 4, according to treatment groups defined in section 1.3

Demographics for subgroup of patients coming from ACZ885D2203 and/or the subsequent Multiple Patient Program (MPP) treatment plan CACZ885D2207M enrolled in Epoch 3 as well as canakinumab naïve Japanese crFMF patients with non-exon 10 mutations and patients >28 days but <2 years old enrolled in Epoch 2, will be presented separately from the other patients who will be screened and randomized in Epoch 2.

The following common background and demographic variables will be presented:

Continuous variables:

- Age at Baseline
- Height at screening
- Weight at screening
- Body mass index (BMI) at screening
- Time since first symptoms (years)
- number of flares per year
- average duration of flare (days)
- local standardized CRP (mg/l) at baseline
- SAA (mg/l) at baseline

Categorical variables:

- Age categories (≥2-<4 , ≥4-<6, ≥6-<12,≥12-<18, ≥18-<65, ≥65)
- Gender (Male/Female)
- Race (White, Black or African American, Asian, Native Hawaiian or other, Pacific Islander, Unknown, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown, Not reported)
- Prior use of any biologics (No/Yes)
- Prior use of Anakinra (No/Yes)
- Prior use of Tociluzimab (No/Yes)
- Prior use of Etanercept (No/Yes)
- Confirmed gene mutation (TNFRSF1A gene for TRAPS, MEFV gene exon 10 for crFMF, MVK gene for HIDS) (No/Yes)
- Active disease at maximum colchicine dose (for crFMF patients) (No/Yes)
- Intolerance to effective doses of colchicine (for crFMF patients) (No/Yes)

- Type of mutation (display the first 3 most common mutation types then the rest in "Other" category) and allele
- Physician's global assessment of disease activity at baseline (None, Minimal, Mild, Moderate, Severe)
- Physician's severity assessment of disease signs and symptoms at baseline (Absent, Minimal, Mild, Moderate, Severe) for TRAPS: skin rash, musculoskeletal pain, abdominal pain, eye manifestations, for HIDS: lymphadenopathy, aphtous ulcers, abdominal pain, for crFMF: chest pain, abdominal pain, arthralgia/arthritis, skin rash
- Patient's global assessment of disease activity at baseline (None, Minimal, Mild, Moderate, Severe)

Body Mass Index (*BMI*) will be calculated using the following formula:

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

1.6 Patient disposition

The number of patients screened will be presented. In addition, the reasons for screen failures will be provided in listing and will be tabulated. The number and percentage of patients in the randomized set who completed study epochs, and who discontinued the study prematurely (including the reason for discontinuation) will be presented by epoch, `initial randomized treatment and treatment sequence` (defined in section 1.3) and for all patients.

For each protocol deviation, the number and percentage of patients for whom the deviation applies will be tabulated over the study (not by epoch) and will be presented according to randomization treatment in epoch 2.

1.7 Medical history

Any significant prior or active medical condition at the time of signing informed consent will be coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term by initial randomized treatment groups in epoch 2 for the safety set.

1.8 Study medication

The exposure to investigational treatment (number of doses) and duration of exposure (days) during this study will be summarized by cohort, epoch, `initial randomized treatment and treatment sequence` (defined in section 1.3) and listed for the Safety Set.

Duration of exposure will be defined as the time from the first dose of study medication in that epoch to the last visit in the epoch (e.g., treatment epoch 2) +1 in days. For subjects who discontinue, the last visit in the corresponding treatment epoch will be taken into account.

For the final analysis, dose distribution from baseline to end of epoch 4 for each cohort will be displayed.

1.9 Concomitant medication

The number and percentage of patients taking prior/concomitant medication will be summarized by cohort, treatment group in each epoch and ATC class for the safety set. The number and percentage of patients with surgeries and medical procedures will be summarized by cohort, treatment group in each epoch and MedDRA preferred term for the safety set. Prior and concomitant medications will be summarized by treatment group in separate tables. Prior medications will be summarized by initial randomized treatment groups in epoch 2. Concomitant medications will be summarized by epoch and treatment groups (defined in section 1.3). Concomitant medication occurring in follow-up period after discontinuation of study will be listed but not summarized in tables.

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment in epoch 2. 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-baseline and continued into the period where study treatment is administered.

Rescue medications (Corticosteroids and NSAIDS) will also be separately summarized by cohort, epoch, initial randomized treatment and treatment sequence (defined in section 1.3) and ATC class.

Colchicine positive subjects, will be summarized using counts and percentages of subjects who took colchicine at baseline and stopped before or at the end of epoch 2 and subjects who started taking colchicine after day 1 and stopped before or at the end of epoch 2. Subjects will be defined as colchicine positive according to the following:

- Patient who took colchicine continuing after receiving 1st ACZ drug
- Patient who took colchicine after 1st dose of ACZ drug and stopped it after 4 weeks (>4weeks)

Colchicine information for crFMF cohort will be listed.

1.10 Efficacy evaluation

All efficacy evaluations will be performed on the full analysis set (FAS). For the overall analysis from baseline to epoch 4, patients who randomized to Placebo group at the beginning of epoch 2, only data after the first dose of ACZ885 will be included.

1.10.1 Analysis of the primary endpoint

1.10.1.1 Variable(s)

Each cohort (TRAPS, HIDS, crFMF) of the study will have its own primary efficacy variable analyzed separately and independently of the other cohorts. The primary efficacy variable of the randomized treatment epoch (Epoch 2) and for the overall study is the proportion of responders within each cohort, where a responder in epoch 2 is defined as a patient who has

resolution of its index disease flare at Day 15 and does not experience a new flare during the 16 weeks following randomization.

Resolution of the index flare (initial flare at the time of the randomization) is defined at the Day 15 visit as:

- PGA < 2 and CRP within normal range (≤10 mg/L) or reduction of ≥ 70% from baseline

Absence of new flares over the first 16 weeks, where new flare is defined from the time of the resolution of the index flare as:

- Physician's Global Assessment (PGA) ≥2, and
- CRP ≥ 30 mg/l

In the randomized treatment epoch (Epoch 2), patients needing dose escalation in the canakinumab arms, or escape from Placebo and receive open-label canakinumab, or are discontinued from the study due to any reason prior to evaluating the primary endpoint will be considered as non-responders. Local standardized CRP results shall be used for responder evaluation. For all visits, if local standardized CRP result is missing then the central standardized CRP result should be considered (except when patient discontinued)". Note: the central lab values have to be standardized before they are used for the analysis and standardized value shall be conducted based on the SI normal range of 0.0-10.0 mg/l. Values in the original measurement unit (OMU), denoted x have been transformed into standardized values, denoted xref, as xref= 10 × [(x – minOMU) / rangeOMU], where minOMU and rangeOMU are minimum value and range on the OMU respectively.

Patient receiving an add-on dose before day 15 will not be considered as having resolution of the index flare at day 15.

1.10.1.2 Statistical model, hypothesis, and method of analysis

The primary hypothesis tested will be the superiority of canakinumab dose (150mg sc [or 2mg/kg] q4w) relative to placebo with respect to the proportion of responders in the randomized treatment epoch (Epoch 2), where a responder is defined as a patient who has resolution of its index disease flare and does not experience a new flare during the 16 weeks following randomization. The hypothesis within each cohort will be tested at a one-sided 2.5% level.

The statistical hypothesis is that there is no difference in the proportion of patients w ho respond at Week 16 with the canakinumab dose 150 mg s.c. (or 2mg/kg) q4w versus placebo. Let p_{jk} denote the proportion of responders at Week 16 for treatment group j and cohort k, k = 1, 2, 3 for each of the cohorts and j=0, 1 where

- 0 corresponds to placebo,
- 1 corresponds to canakinumab 150mg q4w.

The following hypotheses will be tested

- H_{1k}: $p_{1k} - p_{0k} = 0$ versus H_{A1k}: $p_{1k} - p_{0k} > 0$,

In other words:

- H_1: canakinumab 150 mg q4w is not different to placebo with respect to responder rate at Week 16.

Canakinumab treatment group will be compared to placebo with respect to the proportion of responders at Week 16 using the Fisher's exact test. The proportion of responders, as well as the odds ratio and risk difference with corresponding 95% confidence interval will be presented. The 95% confidence interval for the proportions will be calculated using exact (Clopper – Pearson) method.

1.10.1.3 Handling of missing values/censoring/discontinuations

Patients needing dose escalation in the canakinumab arms, or who escape from placebo to canakinumab in the randomized treatment epoch (Epoch 2), or discontinued from the study due to any reason prior to evaluating the primary endpoint will be considered as non-responders in epoch 2.

1.10.1.4 Supportive analyses

The primary analysis in the randomized treatment epoch will be repeated where definition of the resolution of the index flare and new flare definition will be derived from the centralized SAA values. Resolution of the index flare (initial flare at the time of the randomization) is defined at the Day 15 visit as:

- PGA < 2, and SAA within normal range (≤10 mg/L) or reduction of ≥ 70% from baseline

Absence of new flares over the first 16 weeks, where new flare is defined from the time of the resolution of the index flare as:

- PGA ≥2, and SAA ≥ 30 mg/l

If SAA value is missing for the response assessment at scheduled visit then no imputation will be applied and response will be missing.

1.10.1.5 Sensitivity analyses

The primary analysis in the randomized treatment epoch will be repeated on the Full Analysis Set where patients receiving a single add-on injection before Day 15 will be excluded. This implies that the following patients will be excluded;

- patients receiving add-on injection based on criterion from Day 8 to Day 14(persistent PGA ≥2, or CRP persistent >10 mg/L with less than 40% reduction from baseline from Day 8 to Day 14),
- patients receiving a single add-on injection despite they don't fulfill criterion for add-on injection from Day 8 to Day 14.

A second sensitivity analysis will be performed on the Full Analysis Set where patients receiving a single add-on injection despite they don't fulfill criterion for add-on injection from Day 8 to Day 14 will be excluded.

A third sensitivity analysis will be performed where the primary analysis in the randomized treatment epoch will be repeated on Full Analysis Set where patients receiving a single add-on

injection before Day 15 will be considered as responders except if new flare occurs from Day 15 onward in Epoch 2.

In additionally, two more sensitivity analysis will be performed where the primary efficacy analysis on week 16 in the randomized treatment epoch will be repeated on Full Analysis Set

- Where only local values will be used and if missing local CRP values at visit 102 then no resolution of the index flare will be considered.
- Where only central values will be used and if missing central CRP values at visit 102 then no resolution of the index flare will be considered.

1.10.2 Analysis of secondary variables

Secondary efficacy variables will be analyzed separately for each independent cohort (TRAPS, HIDS, crFMF).

The secondary efficacy objectives will be evaluated by assessing the efficacy of canakinumab (q4w in the randomized treatment epoch, and q8w in the randomized withdrawal epoch) as compared to placebo and will be analyzed by cohort. All secondary efficacy objectives will be included in the closed testing procedure.

- to evaluate the percentage of patients who achieve a PGA < 2 at Week 16
- to evaluate the percentage of patients with the serologic remission at Week 16 (defined as C-reactive protein [CRP] ≤10 mg/L)
- to evaluate the percentage of patients with normalized Serum Amyloid A (SAA) level at Week 16 (defined as SAA ≤10 mg/L)
- to evaluate the percentage of canakinumab responders in Epoch 2 who maintain clinically meaningful response (absence of new flares) when switched to a canakinumab every 8 weeks regimen compared to placebo (Epoch 3).

1.10.2.1 Testing strategy

The following hypotheses will be included in the closed testing procedure, and type-I-errors will be set such that a family-wise type-I-error rate of 2.5% is kept (one sided tests)

- Primary objective: H_1.

Secondary objectives:

- H_2: Canakinumab 150mg q4w is not different to placebo with respect to the percentage of patients with PGA < 2 at Week 16.
- H_3: Canakinumab 150mg q4w is not different to placebo with respect the percentage of patients with CRP ≤10mg/L at Week 16.
- H_4: Canakinumab 150mg q4w is not different to placebo with respect the percentage of patients with SAA ≤ 10mg/L at Week 16.
- H_5: Canakinumab 150mg q8w is not different to placebo with respect to the percentage of responders (absence of new flares) at Week 40.

If the primary objective is achieved, all secondary endpoints in the randomized treatment epoch (Epoch 2) will be assessed. If all secondary objectives are achieved in the randomized treatment epoch (Epoch 2), then the secondary objective in the randomized withdrawal epoch will be tested. The 95% confidence interval for the proportions will be calculated using exact (Clopper –Pearson) method.

Physician's global assessment of disease activity (PGA)

PGA is based on a 5-point scale for disease associated signs and symptoms:

0 (=none/no), 1 (=minimal), 2 (=mild), 3 (=moderate), and 4 (severe).

Frequency tables will be provided by analysis visit and randomized treatment groups for each cohort. Between-treatment differences for the proportion of patients with PGA < 2 at Week 16 will be analyzed using a logistic regression model with treatment group, and baseline PGA as explanatory variables for each cohort. All randomized patients at start of Epoch 2 will be considered for this analysis. Patients needing dose escalation in the canakinumab arms, or who escape from placebo arms to canakinumab in the randomized treatment epoch (Epoch 2), or discontinued from the study due to any reason prior evaluating the endpoint at week 16, will be considered as having PGA ≥ 2. If the logistic regression model has difficulty converging due low or high response rates, then Firth's method will be used in the logistic regression model. If the convergence issue is still not resolved then Canakinumab treatment group will be compared to placebo with respect to the proportion of patients with PGA < 2 at Week 16 will be analyzed using the Fisher's exact test.

Serological remission

Serological remission is defined as CRP ≤ 10mg/L. Between-treatment differences for the proportion of patients with CRP ≤ 10mg/L at Week 16 will be analyzed using a logistic regression model with treatment group, and baseline CRP values as explanatory variables for each cohort. All randomized patients at Epoch 2 will be considered for this analysis. Patients needing dose escalation in the canakinumab arms, or who crossed-over from placebo arms to canakinumab in the randomized treatment epoch (Epoch 2), or discontinued from the study due to any reason prior evaluating the endpoint at week 16, will be considered as having CRP > 10mg/L. If the logistic regression model has difficulty converging due low or high response rates, then Firth's method will be used in the logistic regression model. If the convergence issue is still not resolved then the canakinumab treatment group will be compared to placebo with respect to the proportion of patients with CRP ≤ 10mg/L at Week 16 will be analyzed using the Fisher's exact test.

Normalization of SAA

Normalization of SAA is defined as SAA ≤ 10mg/L. Between-treatment differences for the proportion of patients with SAA ≤ 10mg/L at Week 16 will be analyzed using a logistic regression model with treatment group, and baseline SAA values as effect for each cohort. All randomized patients at Epoch 2 will be considered for this analysis. Patients needing dose escalation in the canakinumab arms, or who crossed-over from placebo arms to canakinumab

in the randomized treatment epoch (Epoch 2), or discontinued from the study due to any reason prior evaluating the endpoint at week 16, will be considered as having SAA > 10mg/L. If the logistic regression model has difficulty converging due low or high response rates, then Firth's method will be used in the logistic regression model. If the convergence issue is still not resolved then the Canakinumab treatment group will be compared to placebo with respect to the proportion of patients with SAA ≤ 10mg/L at Week 16 will be analyzed using the Fisher's exact test.

Maintenance of clinically meaningful response

Responder in the Randomized withdrawal epoch (epoch 3) is defined as no flare between week 16 and week 40. The canakinumab 150mg q8w treatment group will be compared to placebo with respect to the proportion of responders at Week 40 using the Fisher's exact test. Only canakinumab responders in Epoch 2 and re-randomized at week 16 will be considered in the analysis. The proportion of responders, as well as the odds ratio (if estimable) and risk difference with corresponding 97.5% confidence interval will be presented. Canakinumab responders at end of epoch 2 needing dose escalation in the canakinumab arm, or who crossed-over from placebo arm to canakinumab in Epoch 3, or discontinued from the study due to any reason in epoch 3 will be considered as non-responders in epoch 3.

1.10.3 Subgroup analyses

Primary and secondary efficacy analyses will be repeated by subgroup of prior use of any biologics (No/Yes) and by age groups (<18 years old and ≥ 18 years old).

Primary and secondary efficacy endpoints based on week 16 will be repeated by Colchicine subgroup as defined below for crFMF cohort only. Colchicine is defined with ATC code: M04AC01.

Two groups will be defined:

Colchicine negative defined as :

- Colchicine Naïve patients (no colchicine before or after treatment)
- Patient who took colchicine before and stopped before receiving ACZ drug
- Patient who took colchicine before and stopped within 4 weeks after 1st dose of ACZ drug (≤4weeks)

Colchicine positive defined as :

- Patient who took colchicine continuing after receiving 1st ACZ drug
- Patient who took colchicine after 1st dose of ACZ drug and stopped it after 4 weeks (>4weeks)

1.10.3.1 Additional analyses

Number and percentage of patients with resolution of index flare at day 15 based on status of receiving add-on dose before day 15 will be presented by initial randomized treatment. In addition, number and percentage of responders at day 29 for non-responders at day 15 based on their value at day 15 and by status of up-titration before day 29 will be presented.

1.10.4 Exploratory analysis

An exploratory analysis will be performed where the primary and secondary efficacy analysis on week 16 in the randomized treatment epoch will be repeated on Full Analysis Set where patients initially randomized to ACZ will be considered as responder if : Resolution of index flare at day 15 and no flare after day 15 or for those who have been up-titrated to 300 mg before day 29, have resolution of index flare at day 29 (PGA < 2 and CRP within normal range (≤10 mg/L) or reduction of ≥ 70% from baseline) and no flare after day 29.

1.10.5 Exploratory efficacy variables

Exploratory efficacy variables will be analyzed separately for each independent cohort (TRAPS, HIDS, crFMF).

Inflammatory parameters (CRP, SAA)

CRP and SAA will be summarized descriptively by analysis visit for each cohort, by epoch and treatment groups (as defined in section 1.3).

In addition, the number and percentage of patients with CRP ≤10mg/L, SAA ≤10mg/L will also be presented.

Number and percentage of patients with CRP ≤10mg/L, CRP > 10- <15 mg/L, CRP ≥15-<30 mg/L, CRP≥30 mg/L at day 15 will be presented by status of resolution of index flare and initial randomized treatment.

Number and percentage of patients with CRP ≤10mg/L, CRP > 10- <15 mg/L, CRP ≥15-<30 mg/L, CRP≥30 mg/L at day 29 will be presented for patients initially receiving ACZ and having up-titration before day 29 by disease cohorts.

In addition, number and percentage of patients with the following categories will be summarized for CRP assessment before day 15, at day 15 and day 29 by initial randomized treatment by disease cohorts.

- CRP ≤10mg/L
- CRP reduction less than 40% from baseline
- CRP reduction of ≥ 70% from baseline
- CRP reduction of ≥ 40% from baseline

In the final analysis, summary tables of CRP and SAA after patients taking ACZ885 will be shown by visit, from Baseline to last visit in Epoch 4.

PGA and PPGA Disease Activity, Key disease specific signs and symptoms

The efficacy outcomes measured on Likert scale, such as physician's global assessment of disease activity, physician's severity assessment of disease signs and symptoms, will be presented in frequency tables by analysis visit for each cohort, epoch and treatment groups (as defined in section 1.3).

Between-treatment differences for the proportion of patients with no disease activity based on PGA (PGA<1), no disease activity (rate overall severity<1) based on PPGA at Week 16 will be analyzed using a Fisher's exact test for each cohort, by randomized treatment group.

Patients needing dose escalation in the canakinumab arms, or who escape from placebo arms to canakinumab in the randomized treatment epoch (Epoch 2) or discontinued from the study due to any reason prior evaluating the endpoint at week 16, will be considered as having PGA ≥1 and PPGA≥1.Patient/parent's global assessment of disease activity (PPGA) will also be summarized for weekly averages using summary statistics. Week 0 will be average of PPGA score from day -7 to day 1, week 1 will be average of score from day 2 to day 7, week 2 will be average of score from day 8 to day 14 and so on.

In addition, Spaghetti plot will be provided by subject and cohort and initial randomized treatment for PGA assessment and Physician's severity assessment of disease signs and symptoms

In the final analysis, shifts in PGA score from baseline to end of Epoch 4 by treatment group for each cohort will be shown in figures. , Summary tables of PGA after patients taking ACZ885 will be shown by visit, from Baseline to last visit in Epoch 4.

Episodes of Fever

Number and duration of fever episodes collected in patient's diaries will be summarized within each cohort, epoch and treatment group (as defined in section 1.3). Plots of fever episodes per patient over time (displaying frequency and duration) and treatment group will also be presented. Treatment difference for time to first resolution of fever will be analyzed using a Cox proportional hazard regression model. The Kaplan-Meier estimates of the proportion of patients with first resolution of fever along with the associated 95% confidence intervals using the Greenwood's formula will be provided.

Rescue medication

Corticosteroids levels will be summarized descriptively by analysis visit for each cohort and by treatment group (as defined in section 1.3). In addition, the number and percentage of patients who reduce their corticosteroids maintenance dose at Week 16 compared to baseline, patients who take corticosteroids rescue medication and patients who take only NSAIDs rescue medication during the study, patients who take steroid level >0.2 mg/kg/day will also be presented. Between-treatment differences for the proportion of patients who are able to reduce their corticosteroids at Week 16 will be analyzed using a Fisher's exact test for each cohort. The analysis will only include subjects who were receiving corticosteroids at baseline.

Rescue medications are not collected visit wise in the study and are collected in summary page as part of concomitant medications. Rescue medications will be mapped to visits. Rescue medications shall be assigned to visit based on start and end date of the medication and corresponding visit date. For example, if visit date for visit 103 lies between start and end date of "VALISONE-G" corticosteroid then dose level of this concomitant medication will be assigned to visit 103. If there are more than one dose that are assigned to same visit then these

doses shall be added after converting the units to mg/kg/day. If there are no records of rescue medication for any visit then it shall be considered as 0 mg/kg/day dose.

Blinded escape

The number and percentage of patients who require blinded escape from Days 8 to 28 will be summarized by cohort and randomized treatment group.

Auto-Inflammatory Disease Activity Index (AIDAI)

Symptoms evaluated in the AIDAI diary will be summarized with each cohort and epoch (2 and 3) and by treatment group (as defined in section 1.3) for monthly score as sum of scores over a month. Spaghetti plot will be provided by subject and cohort and initial randomized treatment.

[redacted]

Time to first new flare in the randomized withdrawal epoch (Epoch 3)

Time to first new flare in Epoch 3 will be analyzed for patients re-randomized at the start of epoch 3. The two treatment groups (150mg q8w and placebo) will be compared using a one-sided log-rank test at the 2.5% significance level. The hazard ratio and its associated 95% two-sided confidence intervals will be estimated. Kaplan-Meier estimates of the probability to experience a flare event will be calculated from the start of the randomized withdrawal epoch. 95% confidence intervals using Greenwood's formula will be provided.

Patients who discontinued the study in epoch 3, or having an up-titration or escape from placebo group to canakinumab arm will be counted as having a flare in epoch 3. In this case the date of the premature subject withdrawal (PSW) visit, or resp. time of up-titration or escape is considered as the end date for the calculation of time to flare.

SF-12 Health Survey (SF-12)

SF-12 scores will be summarized (descriptively) by epoch (2 and 3), analysis visit, `initial randomized treatment and treatment sequence` (as defined in section 1.3) within each cohort. Only patients ≥18 years of age at baseline will be part of the analyses.

SF-12 measurements consists of 12 questions over eight subscales (physical function, pain, general and mental health, vitality, social function, physical and emotional health). The subscales can be aggregated to derive a physical-component summary score (PCS) and a mental-component summary score (MCS).

The score will be summarized for each subscale and for PCS and MCS.

Child Health Questionnaire – Parent Form 50 (CHQ-PF50)

Descriptive statistics will be used to summarize patient responses on the CHQ-PF50© Questionnaire by epoch (2 and 3), analysis visit, `initial randomized treatment and treatment sequence` (as defined in section 1.3), total score (Physical (PhS) and Psychosocial

(PsS) scores) and by domain within each cohort. Only patients >5 <18 years of age at baseline are included.

Sheehan Disability Scale (SDS v3)

SDS score by domain and global functional impairment score will be summarized by epoch (2 and 3), analysis visit, `initial randomized treatment and treatment sequence` (as defined in section 1.3) within each cohort.

Number of flares

The number of new flares by patient will be summarized by epoch and treatment arms within each cohort.

Disease-associated genetic mutations

Relationships between disease-associated genetic mutations and CRP/SAA/PGA values at Day 15 on patients randomized to Canakinumab will be analyzed by cohort. T-test will be used for mean comparison between genetic mutations for CRP and SAA, and wilcoxon rank sum test will be used for mean comparison between genetic mutations for PGA. Mean CRP, SAA, PGA at Day 15 were compared between

For cr-FMF cohort

(i) all M694V gene vs overall cr-FMF canakinumab treated patients
(ii) all M694V gene vs non-M694V gene
(iii) M694V heterozygous vs homozygous

For HIDS cohort

(i) all V377I gene vs overall HIDS canakinumab treated patients
(ii) all V377I gene vs non-V377I gene
(iii) V377I heterozygous vs homozygous

For TRAPS cohort

(i) all R92Q gene vs overall TRAPS canakinumab treated patients
(ii) all R92Q gene vs non-R92Q gene
(iii) R92Q heterozygous vs homozygous

In the T-test procedure, Pooled and Satterthwaite methods for the p-value were used depending on the test on equality of variances.

In the Npar1way procedure, p-value from Exact test was taken given the relatively small sample size of patients.

1.11 Pharmacokinetic

Pharmacokinetic (PK) concentrations will be summarized by epoch by means of arithmetic and geometric mean, median, standard deviation, minimum and maximum, coefficient of variation for arithmetic and geometric mean, the number of non-missing data points and the number of data points greater than zero. Sample number, date, scheduled timepoint, actual time of sample and days post dose (elapsed time) will also be listed.

1.12 Pharmacodynamics

Total IL-1β

Total Interleukin-1 beta (IL-1β) summary statistics (arithmetic and geometric mean, median, standard deviation, minimum and maximum, coefficient of variation for arithmetic and geometric mean, the number of non-missing data points and the number of data points greater than zero) will be displayed by epoch. Sample number, date, scheduled timepoint and actual time of sample will be listed.

1.12.1 Pharmacogenetics

Sample number, date, scheduled timepoint and actual time of sample will be listed.

1.13 Safety evaluation

All safety evaluations will be performed on the Safety set. For the overall analysis from baseline to epoch 4, patients who randomized to Placebo group at the beginning of epoch 2, only data after the first dose of ACZ885 will be included.

1.13.1 Adverse events

Adverse events will be coded using the MedDRA dictionary that provides the primary system organ class and preferred term information.

Adverse events will be summarized by presenting, for each cohort, epoch, `initial randomized treatment and treatment sequence` (as defined in section 1.3), the number and percentage of patients having any adverse event, having any adverse event in each primary system organ class and having each individual adverse event based on the preferred term. All other information collected (e.g. severity, relationship to study treatment) will be tabulated and listed as appropriate.

Adverse events will also be summarized by standardized MedDRA query (SMQ).

Exposure adjusted incidence rate of adverse events by primary system organ class and preferred term will be presented by epoch and according to the actual dose the patient receives.

Deaths, serious adverse events, and adverse events leading to discontinuation of study treatment will be summarized by primary system organ class and preferred term and listings will be provided.

Adverse events of special interest including identified and potential risks and adjudicated malignancy and infection events will be listed and summarized for each cohort, epoch and treatment group (as defined in section 1.3).

In addition, summary of adverse events and serious adverse events will be presented in combining the three cohorts. Adverse events occurring in follow-up period after discontinuation of study will be listed but not summarized in tables.

For the final analysis, AE/SAE will be reported using data after patients taking ACZ885 starting from epoch 2 to end of epoch 4.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on any ACZ group adverse events which are not serious adverse events with an incidence greater than 5% and on any ACZ group 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 ≤ 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".

1.13.2 Local injection site tolerability

Local injection site tolerability will be assessed on the injection site (separately from the adverse event page). Each patient will be classified into one of the following four categories (based on AE ATC grade):

1. No tolerability reactions at any time in the trial.
2. A mild reaction (grade 1) observed on at least one occasion but no moderate or severe/ potentially life threatening reactions.
3. A moderate reaction (grade 2) observed on at least one occasion but no severe/ potentially life threatening reactions.
4. A severe (grade 3) or potentially life threatening (grade 4) reaction observed on at least one occasion.

The number and percentage of patients in each category will be presented for each cohort, epoch, `initial randomized treatment and treatment sequence` (as defined in section 1.3). In addition, summary of pre-specified symptoms (Erythema/Redness, Tenderness, Induration/Swelling, Pain) will be provided. All details of injection site reactions will be listed.

1.13.3 Laboratory data

Laboratory parameters will be summarized by presenting descriptive statistics for the absolute values, change from baseline (and from each start of epoch) for each cohort, epoch, analysis visit and treatment group (as defined in section 1.3). Change from baseline (resp. start of epoch) will only be summarized for patients with both baseline (resp. start of epoch) and post baseline values in each epoch. There will be multiple “baseline” as one will be defined for each start of epoch. All information collected will be listed by patient and abnormal values will be flagged. In addition, shift tables based on normal ranges and incidence rates of notable abnormalities will be presented.

Creatinine clearance will be also be summarized by subgroup of Colchicine for crFMF disease cohort. Creatinine clearance will also be summarized by subgroup of CKD categories defined at baseline derived using eGFR value as below:

CKD Stage 1: >=90 ml/min/1.73m2

CKD Stage 2: 60-<90 ml/min/1.73m2

CKD Stage 3a-b: 30-<60 ml/min/1.73m2

CKD Stage 4-5: <30 ml/min/1.73m2

Shift in CKD stage from baseline to end of epoch 2, epoch 3 and epoch 4 will be summarized for crFMF disease cohort patients.

Notable laboratory abnormalities in adult patients (≥ 18 years of age)

Post-baseline values will be flagged as notable abnormalities as follows:

Biochemistry

1. ALT (SGPT): >3x, 5x, 10x, and 20x Upper Limit of Normal (ULN)[1]
2. AST (SGOT): > 3x, 5x, 10x, and 20x ULN[1]
3. Elevation of AST and/ or ALT (> 3xULN) accompanied by elevated bilirubin (> 1.5xULN, > 2xULN)[1]
4. Any elevations of bilirubin; elevated total bilirubin (TBL) to > 2x ULN[1]
5. Any elevations of ALP >1.5x ULN
6. Gamma-Glutamyltransferase (GGT): > 3x ULN
7. Creatinine (serum): ≥ 3x ULN
8. Creatinine clearance (CrCl) (Cockroft-Gault formula)[2]: ≥ 25% decrease from baseline
9. Triglycerides: >5x ULN

Hematology

1. Hemoglobin: ≥20 g/L decrease from baseline,
   <100 g/L
2. Platelet count[3]
   a. CTC Grade 1: <Lower Limit of Normal (LLN) – 75 x 10^9/L
   b. CTC Grade 2: <75 – 50 x 10^9/L
   c. CTC Grade 3: <50 – 25 x 10^9/L
   d. CTC Grade 4: <25x 10^9/L
3. White blood cell count[3]
   a. CTC Grade 1: <LLN – 3 x 10^9/L
   b. CTC Grade 2: <3 – 2 x 10^9/L
   c. CTC Grade 3: <2 – 1 x 10^9/L
   d. CTC Grade 4: <1 x 10^9/L
4. Absolute neutrophils
   a. CTC Grade 1: <LLN – 1.5 x 10^9/L

b. CTC Grade 2: <1.5 – 1 x 10^9/L
c. CTC Grade 3: <1 – 0.5 x 10^9/L
d. CTC Grade 4: <0.5 x 10^9/L

5. Absolute lymphocytes: <LLN
6. Absolute eosinophils: ≥ 2.5x, ≥ 3x ULN

Urinalysis
Protein urine dipstick: ≥ ++

Notable laboratory abnormalities in pediatric patients (< 18 years of age)

Post-baseline values in pediatric patients (at the time of the assessment) will be flagged as notable abnormalities as follows:

Biochemistry
1. ALT (SGPT): > 3x, 5x, 10x, and 20x Upper Limit of Normal (ULN)[1]
2. AST (SGOT): > 3x, 5x, 10x, and 20x ULN[1]
3. Elevation of AST and/ or ALT (> 3xULN) accompanied by elevated bilirubin (> 1.5xULN, > 2xULN)[1]
4. Any elevations of bilirubin; elevated total bilirubin (TBL) to > 2x ULN[1]
5. Any elevations of ALP >1.5x ULN[1]
6. GGT: ≥ 3x, 5x ULN
7. Creatinine (serum): ≥ 1.5x ULN
8. Creatinine clearance (Schwartz formula§): ≥ 25% decrease from baseline, ≥2 consecutive visits
9. Total Cholesterol: ≥ 1.5xULN
10. Triglycerides: ≥ 5.7 mmol/L
11. Creatinine clearance (Schwartz formula[4]): ≥ 25% decrease from baseline for ≥3 months in duration in combination with protein urine dipstick resulting in new protein ≥1+, ≥3 months in duration

Hematology

1. Hemoglobin: ≥20 g/L decrease from baseline,

<85 g/L (patients < 16 years of age) or <100 g/L (patients ≥ 16 years of age)

2. Platelet count[3]

- CTC Grade 1: <Lower Limit of Normal (LLN) – 75 x 10^9/L
- CTC Grade 2: <75 – 50 x 10^9/L
- CTC Grade 3: <50 – 25 x 10^9/L
- CTC Grade 4: <25x 10^9/L

3. White blood cell count[3]

- CTC Grade 1: <LLN – 3 x 10^9/L
- CTC Grade 2: <3 – 2 x 10^9/L

- CTC Grade 3: <2 – 1 x 10^9/L
- CTC Grade 4: <1 x 10^9/L

4. Absolute neutrophils

- CTC Grade 1: <LLN – 1.5 x 10^9/L
- CTC Grade 2: <1.5 – 1 x 10^9/L
- CTC Grade 3: <1 – 0.5 x 10^9/L
- CTC Grade 4: <0.5 x 10^9/L

5. Absolute lymphocytes: <LLN

6. Absolute Eosinophils: ≥ 1.1 x ULN, ≥0.45 x 10^9/L

Urinalysis

- Protein urine dipstick: ≥+ for ≥3 months in duration

[1] Adapted from FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009)

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

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

[3] Common Terminology Criteria for Adverse Events, US Department of Health and Human Services (v4.03: 14-Jun-2010)[4] Creatinine clearance was derived using the following formula:

CrCl (mL/min/1.73m2) = [0.413 x length (cm)/ (serum creatinine mg/dl)] (Schwartz et al. 2009).

1.13.4 Vital signs

Vital signs will be summarized by presenting descriptive statistics for the absolute values and changes from baseline (and from each start of epoch) for each cohort, epoch, analysis visit and treatment group (as defined in section 1.3). All information collected will be listed by patient and abnormal values will be flagged

Notable vital signs abnormalities in adult patients (≥ 18 years of age)

Post-baseline vital signs will be flagged as notable abnormalities as follows:

1. Systolic/Diastolic blood pressure: ≥25% decrease or ≥25 % increase from baseline
2. Pulse: ≥ 110 bpm with ≥15% change from baseline, or < 50 bpm with ≥15% change from baseline

Notable vital signs abnormalities in pediatric patients (< 18 years of age)

Post-baseline vital signs in pediatric patients (at the time of the assessment) will be flagged as notable abnormalities as follows:

1. Systolic blood pressure (mmHg): >ULN and increased >20 in change from baseline or <LLN and decreased >20 in change from baseline
2. Diastolic blood pressure (mmHg): >ULN and increased >20 in change from baseline or <LLN and decreased >20 in change from baseline
3. Pulse (bpm): >ULN and increased >20 in change from baseline or <LLN and decreased >20 in change from baseline

Blood pressure normal range for patients >28 days but <18 years old are listed in below table:

Table 1-3 Blood pressure normal range in pediatric population according to current age

Age	SBP	DBP	Pulse
0 - 1 months[#]	45-80	33-52	93-182
>1 - 3 months[#]	65-85	35-55	120-178
>3 - 6 months[#]	70-90	35-65	107-197
>6 -12 months[#]	80-100	40-65	108-178
>12 months- 2 years[#]	80-100	40-70	90-152
> 2 years - 5 years	100-115	65-75	80-130
> 5 years -12 years	110-125	70-80	70-115
> 12 years -18 years	120-135	75-85	60-100

Age is age at the time of the visit.

[#]Reference values according to website: http://www.sickkids.ca/Nursing/Education-and-learning/Nursing-Student-Orientation/module-two-clinical-care/vitals/.

ECG

Listings and table will be provided for notable ECG abnormalities. Summary statistics will be presented for ECG variables by epoch, analysis visit and treatment group for each cohort.

1.13.5 Immunogenicity

A listing for each cohort will be presented for patients who develop immunogenicity.

1.13.6 Liver safety monitoring

A listing for each cohort will be presented for patients with liver events.

1.14 Interim analyses

Contingency Analysis

If there is any delay in the enrollment of the patients in one of the cohorts in the randomized treatment epoch i.e. it takes more than 24 weeks to recruit patients in one of the cohorts, then an interim analysis performed within each cohort would be considered. The decision to perform

this interim analysis would be taken jointly between the indication-specific lead investigators and Novartis.

- If overall enrollment time has surpassed 24 weeks,
- AND If >2/3 patients are enrolled in the slowest enrolling cohort.

However, due to the low number of patients in the slowest enrolling cohort, the interim analysis will not be sufficiently powered to detect statistically significant differences. Thus only descriptive analysis would be performed in this cohort and these results will complete the dossier with the final results of the two cohorts where all patients have been recruited.

Primary efficacy analysis

In order to support regulatory filing, the analyses of the primary and all Week 16 secondary efficacy variables will be performed after all subjects have completed the final visit of the randomized treatment epoch (Epoch 2) of the study (Day 113). These results will be presented in a first Clinical Study Report (CSR).

40-week interim analysis

An interim analysis is planned at the end of the randomized withdrawal epoch (Epoch 3). An Interim Analysis CSR may be prepared to support health authority interactions, as necessary. The final long-term safety analyses involving data from all 4 epochs will be performed after all patients have completed the final visit of the trial (Day 785) and will be presented in the final CSR.

1.15 Determination of sample size

The primary efficacy objective in the randomized treatment epoch and for the overall study is to compare canakinumab treatment to placebo with respect to the proportion of responders at Week 16 using the Fisher's exact test. The proportion of responders, as well as the odds ratio (if estimable) and risk difference with corresponding 97.5% confidence interval will be presented. [redacted] Since a 20% screening failure rate is expected, it is estimated that approximately [redacted] patients have to be screened.

Nquery Advisor® software version 7.0 was used.

2 Clinical Study Report - Appendix 16.1.9 Documentation of statistical methods

2.1 Analysis visit windows

Baseline/ First day in Epoch 2

For canakinumab naïve Japanese crFMF patients with non-exon 10 mutations and patients >28 days but <2 years old, the date of baseline is equal to the first date of dosing.

For patients who are randomized in epoch 2 then date of baseline is equal to the first date of dosing on or after the date of randomization (Visit 101).

For laboratory and vital signs evaluations the latest value before start of treatment in Epoch 2 was taken as baseline in case of missing baseline.

First day in Epoch 3

For patients who roll-over from study ACZ885D2203/D2207M, the date of baseline is equal to the first date of dosing.

For canakinumab patients in epoch 2 who are responder at week 16, the first day in epoch 3 is equal to the first date of dosing on or after the date of re-randomization (Visit 201).

For the other patients, the first day in epoch 3 is equal to the first date of dosing at visit 201.

First day in Epoch 4

For all patients, the first day in epoch 4 is equal to the first date of dosing at visit 301.

Time visit window

The visit numbers as reported in the CRF were used except for end of study/epoch visit (visit=199, 299, 399), which were mapped according to Table 2-1.

Table 2-1 Visit window definition

Epoch	Analysis Visit	Visit window (days) for patients who entered epoch 2	Visit window (days) for patients who directly entered epoch 3
2	Day 15 (Week 3)	2 – 18	–
2	Day 29 (Week 5)	19 – 32	–
2	Day 57 (Week 9)	33 – 60	–
2	Day 85 (Week 13)	61 – 88	–
2	Day 113 (Week 17)	89 – 116	–
3	Day 141 (Week 21)	117 – 144	2 – 32
3	Day 169 (Week 25)	145 – 172	33 – 60
3	Day 197 (Week 29)	173 – 200	61 – 88
3	Day 225 (Week 33)	201 – 228	89 – 116
3	Day 253 (Week 37)	229 – 256	117 – 144
3	Day 281 (Week 41)	257 – 284	145 – 172
4	Day 337 (Week 49)	285 – 340	173 – 228
4	Day 393 (Week 57)	341 – 396	229 – 284
4	Day 449 (Week 65)	397 – 452	285 – 340
4	Day 505 (Week 73)	453 – 508	341 – 396
4	Day 561 (Week 81)	509 – 564	397 – 452
4	Day 617 (Week 89)	565 – 620	453 – 508
4	Day 673 (Week 97)	621 – 676	509 – 564
4	Day 729 (Week 105)	677 – 732	565 – 620
4	Day 785 (Week 113)	>733	>620

For subjects who prematurely discontinue between two scheduled visits, the data at the end of study/epoch visit will be re-aligned to the visit which belongs to the associated visit window. If the early termination visit is mapped to a visit for which the scheduled visit was already performed, then the assigned visit number will be set to the next one. For example if a patient discontinued prematurely at week 8 (assigned based on the visit window above) but already has a value for week 8, then the end of study visit will be set to week 12.