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ACZ885 / Canakinumab

Clinical Trial Protocol CACZ885N2301 / 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

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Table of contents

Table of contents 2
List of tables 5
List of figures 6
List of abbreviations 7
Glossary of terms 9
Protocol summary 13
1 Introduction 17
1.1 Background 17
1.2 Purpose 18
2 Study objectives 19
2.1 Primary objective(s) 19
2.2 Secondary objectives 19
2.3 Exploratory objectives 19
3 Investigational plan 20
3.1 Study design 20
3.1.1 Screening epoch (Epoch 1) 24
3.1.2 Randomized treatment epoch (Epoch 2) 24
3.1.3 Randomized withdrawal epoch (Epoch 3) 27
3.1.4 Open-label treatment epoch (Epoch 4) 28
3.2 Rationale of study design 29
3.3 Rationale of dose/ regimen, route of administration and duration of treatment 29
3.4 Rationale for choice of comparator 30
3.5 Purpose and timing of interim analyses/design adaptations 30
3.6 Risks and benefits 31
4 Population 31
4.1 Inclusion criteria 32
4.1.1 Criteria applicable for all cohorts 32
4.1.2 Criteria applicable for patients with TRAPS (cohort 1) 32
4.1.3 Criteria applicable for patients with HIDS (cohort 2) 32
4.1.4 Criteria applicable for patients with crFMF (cohort 3) 33
4.2 Exclusion criteria 34
5 Treatment 37
5.1 Protocol requested treatment 37
5.1.1 Investigational treatment 37

5.1.2 Additional study treatment 37
5.2 Treatment arms 37
5.3 Treatment assignment, randomization 38
5.4 Treatment blinding 39
5.5 Treating the patient 39
5.5.1 Patient numbering 39
5.5.2 Dispensing the investigational treatment 40
5.5.3 Handling of study treatment 40
5.5.4 Instructions for prescribing and taking investigational treatment 41
5.5.5 Permitted dose adjustments and interruptions of study treatment 41
5.5.6 Rescue medication 41
5.5.7 Concomitant treatment 42
5.5.8 Prohibited Treatment 42
5.5.9 Discontinuation of study treatment 42
5.5.10 Withdrawal of consent 43
5.5.11 Loss to follow-up 43
5.5.12 Emergency breaking of assigned treatment code 44
5.5.13 Study completion and post-study treatment 44
5.5.14 Early study termination 44
6 Visit schedule and assessments 45
6.1 Information to be collected on screening failures 54
6.2 Patient demographics/ other baseline characteristics 54
6.2.1 Determination of tuberculosis status 54
6.2.2 Hepatitis screen, HIV screen 55
6.3 Treatment exposure and compliance 56
6.4 Efficacy 56
6.4.1 Physician's global assessment of Disease activity (PGA) 56
6.4.2 Physician's severity assessment of key disease-specific signs and symptoms 56
6.4.3 Inflammatory markers 57
6.4.4 Resolution of the index flare 57
6.4.5 New disease flare 57
6.4.6 Auto-inflammatory Disease Activity Index (AIDAI) 57
6.4.7 Patient/ Parent's global assessment of disease activity (PPGA) 58
6.4.8 Health-related Quality of Life 58
6.4.9 Appropriateness of efficacy assessments 60

6.5 Safety 60
6.5.1 Physical examination 60
6.5.2 Vital signs 60
6.5.3 Height and weight 61
6.5.4 Laboratory evaluations 61
6.5.5 Electrocardiogram (ECG) 62
6.5.6 Pregnancy and assessments of fertility 62
6.5.7 Appropriateness of safety measurements 63
6.6 Other assessments 63
6.6.1 Resource utilization 63
6.6.2 Pharmacokinetics 63
6.6.3 Pharmacodynamics 64
6.6.4 Pharmacogenetics/pharmacogenomics 64
6.6.5 Immunogenicity 65
6.6.6 Other biomarkers 66
7 Safety monitoring 66
7.1 Adverse events 66
7.2 Serious adverse events 67
7.2.1 Definition of SAE 67
7.2.2 SAE reporting 68
7.3 Liver safety monitoring 69
7.4 Renal safety monitoring 70
7.5 Pregnancy reporting 71
8 Data review and database management 72
8.1 Site monitoring 72
8.2 Data collection 72
8.3 Database management and quality control 73
8.4 Data Monitoring Committee 73
8.5 Adjudication Committee 73
8.5.1 Infection Adjudication Committee 73
8.5.2 Malignancy Adjudication Committee 74
9 Data analysis 74
9.1 Analysis sets 75
9.2 Patient demographics and other baseline characteristics 76
9.3 Treatments 76

9.4 Analysis of the primary variable(s) 76
9.4.1 Variable(s) 76
9.4.2 Statistical model, hypothesis, and method of analysis 77
9.4.3 Handling of missing values/censoring/discontinuations 77
9.4.4 Supportive analyses 77
9.4.5 Sensitivity analyses 78
9.5 Analysis of secondary variables 78
9.5.1 Secondary efficacy variables 78
9.5.2 Exploratory efficacy variables 80
9.5.3 Safety variables 82
9.5.4 Resource utilization 83
9.5.5 Pharmacokinetics 83
9.5.6 Pharmacogenetics/pharmacogenomics 83
9.5.7 Biomarkers 83
9.5.8 PK/PD 84
9.6 Interim analyses 84
9.7 Sample size calculation 84
10 Ethical considerations 85
10.1 Regulatory and ethical compliance 85
10.2 Informed consent procedures 85
10.3 Responsibilities of the investigator and IRB/IEC 86
10.4 Publication of study protocol and results 86
11 Protocol adherence 86
11.1 Protocol Amendments 87
12 References 87
13 Appendix 1: Clinically notable laboratory values and vital signs 89
14 Appendix 2: Liver event and Laboratory trigger definitions and follow-up requirements 92
15 Appendix 3: Blood Collection Log 95
16 Appendix 4: Level of TB risk 96

List of tables

Table 3-1 Criteria for add-on injection or up-titration in Epoch 2 26
Table 5-1 Prohibited treatment 42

Table 6-1 Assessment schedule: Screening epoch (Epoch 1) and randomized treatment epoch (Epoch 2) 46
Table 6-2 Assessment schedule: Randomized withdrawal epoch (Epoch 3) and open-label treatment epoch (Epoch 4)..... 50
Table 7-1 Specific Renal Alert Criteria and Actions..... 71
Table 14-1 Liver event and laboratory trigger definitions..... 92
Table 14-2 Follow up requirements for liver events and laboratory triggers 92
Table 15-1 Blood Collection Log for PK, PD and Immunogenicity Samples..... 95

List of figures

Figure 3-1 Overall study design 22
Figure 3-2 Cohort detail: Screening (Epoch 1) and randomized treatment Epoch 2..... 23
Figure 3-3 Cohort detail: Randomized withdrawal Epoch 3 and open-label treatment Epoch 4 23

List of abbreviations

AE	Adverse Event
AIDAI	Auto-Inflammatory Disease Activity Index
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BCG	Bacillus Calmette-Guérin
b.i.d.	Twice a day
CAN	Canakinumab
CFR	US Code of Federal Regulations
CDS	Core Data Sheet (for marketed drugs)
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CTRD	Clinical Trial Results Database
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
FMF	Familial Mediterranean Fever
GCP	Good Clinical Practice
GTL	Global Trial Lead
HIDS	Hyper IgD Syndrome
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
i.v.	Intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
LFT	Liver function test (raised serum transaminases and/or bilirubin levels)
MedDRA	Medical dictionary for regulatory activities
OC/RDC	Oracle Clinical/Remote Data Capture

o.d.	Once a day
p.o.	Oral(ly)
PGA	Physician's Global Assessment of Disease Activity
PPD	Purified Protein Derivative
PPGA	Patient's/ Parent's Global Assessment of Disease Activity
PSW	Premature Subject Withdrawal
q4w	Every 4 weeks
q8w	Every 8 weeks
QFT-GIT	QuantiFERON®-TB Gold In-Tube
SAE	Serious Adverse Event
SJIA	Systemic Juvenile Idiopathic Arthritis
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TD	Investigational Treatment Discontinuation
TRAPS	TNF-receptor Associated Periodic Syndrome
WHO	World Health Organization

Glossary of terms

Add-on therapy	Possibility for patients based on clinical condition, to receive a single add-on s.c. injection of canakinumab (150 mg s.c. [or 2 mg/kg for patients ≤40 kg]) between Day 8 and Day 28 without unblinding the initial randomized treatment. Add-on therapy can be given only once from Day 8 to Day 28.
Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical Epochs are: screening/recruitment, wash-out, treatment, and follow-up
Flare	A new disease flare is defined from Day 29 inclusive as simultaneous occurrence of a clinical flare and a serological flare defined as follows: • PGA ≥2 (clinical flare) • CRP ≥30 mg/L (serological flare) For patients who achieved resolution of index flare at Day 15, this definition will be applied from Day 15.
Index flare resolution	Resolution of the index flare is defined as PGA <2, and CRP within normal range (≤10 mg/L) or reduction by at least 70% from baseline assessed at Day 15.
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication.
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system.
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.

Premature subject withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy.
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal.
Subject Number	A number assigned to each patient who enrolls into the study
Up-titration	If patient's condition requires dose increase, up-titration will be allowed through IRT at scheduled visits from Day 29 onwards. Up-titration is done stepwise until the maximum dose of canakinumab 300 mg q4w is reached.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Amendment 1

Amendment rationale

Amendment 1 is issued to address the request from the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK to refer to local label requirement for birth control in female of child bearing potential when treated with canakinumab. This non-substantial amendment was first implemented in the UK,

Changes to the protocol

Changes to the protocol are only related to section 6.5.6 Pregnancy and assessments of fertility to reference the use of effective contraception in accordance with locally approved prescribing information.

Amendment 2

Amendment rationale

Amendment 2 is issued to address the request from the Paediatric Committee (PDCO) at the European Medicines in the framework of respective Pediatric Investigational Plans to include patients >28 days in this clinical trial compared to previously ≥2 years of age. Patients >28 days but <2 years old will enter the study directly into the open-label arm of Epoch 2, but won't be considered toward the total number of patients enrolled for the primary efficacy and safety analyses. In addition, this amendment provides more clarity on patient's management for randomized and non-randomized cohorts in accordance with clinical practice.

Changes to the protocol

Changes to the protocol are related to the following sections:

Glossary of terms: updated to provide missing definitions for Add-on therapy, Flare, Index flare resolution and Up-titration.

Protocol summary is updated to reflect changes made to the protocol.

Section 2.2 Secondary objectives and Section 2.3 Exploratory objectives: revised to correct relevant typos and update exploratory objectives to reflect request from PDCO to include patients >28 days but <2 years old.

Section 3.1 Study design and sub-sequent sections are subsequently adjusted:

- to harmonize the study entry time and treatment for the above mentioned PDCO requested population >28 days but <2 years old and Japanese crFMF patients with non-exon 10 mutations;
- to clarify the definition of resolution of the index flare explaining that besides a 70% reduction, a normal CRP level (≤10 mg/L) also indicates serologic resolution;

- to clarify the blinded escape criteria from Day 8 to Day 14 for patients who experience persistent “mild”, “moderate” or “severe” disease activity (i.e., PGA ≥2 [clinical flare]), or CRP persistent >10 mg/L with less than 40% reduction from baseline.

Section 4 Population and sub-sequent sections are revised to reflect the above mentioned PDCO request, and to align threshold for liver function tests (ALT and AST) with clinical notable laboratory values in mentioned in Section 13 Appendix 1.

Section 5 Treatment and sub-sequent sections are clarifying patients’ management for randomized and non-randomized cohorts and treatment blinding according to revisions in Section 3.

Section 6 Visit schedule and assessments and sub-sequent sections are revised to reflect revisions made in Section 3 (criteria for flare definitions).

Section 9 Data analysis and sub-sequent sections are revised to align with revisions made in Section 3.

Section 13 Appendix 1 Clinically notable laboratory values and Appendix 2 are revised to align with criteria used across ACZ885 program.

Changes to the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are substantial and do require IRB/IEC approval prior to implementation.

Protocol summary

Protocol number	CACZ885N2301
Title	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
Brief title	Study of efficacy and safety of canakinumab in patients with Hereditary Periodic Fevers
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine whether canakinumab is able to induce and maintain a clinically meaningful reduction of disease activity after 16 weeks of treatment in a greater proportion of patients with TRAPS, HIDS, or crFMF compared to placebo. It is further to determine whether, in patients responding to the initial dosing regimen, canakinumab will maintain its clinical efficacy if administered at a prolonged dosing interval.
Primary Objective	The primary objective of the randomized treatment epoch and for the overall study is to demonstrate that subcutaneous canakinumab administered every 4 weeks is superior to placebo in achieving a clinically meaningful reduction of disease activity defined as resolution of the index flare at Day 15 and no new disease flares over 16 weeks of treatment.
Secondary Objectives	• To evaluate the percentage of patients who achieve a Physician Global Assessment of Disease Activity (PGA) <2 (“minimal” or “none”) 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 a clinically meaningful response (absence of new flares) when switched to canakinumab every 8 weeks compared to placebo (Epoch 3) • To evaluate the long-term safety and tolerability and immunogenicity of canakinumab • To evaluate the pharmacokinetics/ pharmacodynamics of canakinumab
Study design	This study consists of 3 cohorts (one cohort per condition: TRAPS, HIDS and crFMF), and 4 study epochs. Each cohort will follow the same study design across the 4 epochs: 1. A screening epoch to assess patients’ eligibility of up to 12 weeks duration (Epoch 1) 2. 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 • Open-label treatment 3. A randomized withdrawal epoch (Epoch 3) of 24 weeks

	4. An open-label treatment epoch (Epoch 4) of 72 weeks to collect long-term safety data for canakinumab 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 Epoch 3. Japanese crFMF patients with non-exon 10 mutations and patients >28 days but <2 years old will enter the study in the open-label arm of Epoch 2.
Population	The study population will consist of male and female patients >28 days and with clinically and genetically confirmed Hereditary Periodic Fevers: TRAPS (cohort 1), HIDS (cohort 2), or crFMF (cohort 3).
Inclusion criteria	• Patient's written informed consent (or parent's written informed consent in case of pediatric patient) at screening • Male and female patients at least 2 years of age at the time of the screening visit. Male and female patients >28 days but <2 years old at the time of the screening visit will be enrolled in the open label arm only. • Confirmed diagnosis of TRAPS, HIDS or crFMF at screening • Active flare of TRAPS, HIDS or crFMF as evidenced by "mild", "moderate" or "severe" disease activity (PGA ≥2) at randomization • CRP >10mg/L (normal CRP range ≤10 mg/L) at randomization
Exclusion criteria	• Use of the following therapies (within varying protocol defined timeframes): Corticosteroids (oral prednisone) >0.2 mg/kg/day (or greater than the maximum of 15 mg/day for children over 60 kg), anakinra, canakinumab, rilonacept, tocilizumab, TNF inhibitors, abatacept, tofacitinib, rituximab, leflunomide, thalidomide, cyclosporine, intravenous immunoglobulin, 6-Merceptopurine, azathioprine, cyclophosphamide, or chlorambucil, intra-articular, peri-articular or intramuscular corticosteroid injections, any other investigational biologics • History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in-situ cervical cancer), treated or untreated • Significant medical diseases, including but not limited to the following: a. History of organ transplantation b. Elevated alanine aminotransferase (ALT) ≥3x ULN c. Elevated aspartate aminotransferase (AST) ≥3x ULN d. Increase in total bilirubin defined as per Common Terminology Criteria (CTC) Grade ≥2 e. Serious hepatic disorder (Child-Pugh scores B or C) f. Chronic Kidney Disease as per NKF stages ≥4 g. Thyroid disease h. Diagnosis of active peptic ulcer disease i. Coagulopathy j. Significant CNS effects including vertigo and dizziness • Any conditions or significant medical problems which immunocompromise the patient and/ or places the patient at unacceptable risk for immunomodulatory therapy, e.g. a. Absolute neutrophil count decreased as per CTC Grade ≥1 b. Thrombocytopenia CTC Grade ≥1 c. Any active or recurrent bacterial, fungal (with exception of onychomycosis) or viral infection

	d. HIV infection, Hepatitis B or Hepatitis C infections e. Presence of tuberculosis f. Requirement for administration of antibiotics against latent TB g. Clinical evidence or history of multiple sclerosis or other demyelinating diseases, or Felty's syndrome • Live vaccinations within 3 months prior to the start of the trial, during the trial, and up to 3 months following the last dose
Investigational and reference therapy	• Canakinumab • Placebo
Efficacy assessments	• PGA • Physician's severity assessment of key disease-specific signs and symptoms • Rescue medication use • Review eDiary instructions • Patient/Parent Global Disease Activity (PPGA) • Auto-Inflammatory Disease Activity Index (AIDAI)
Safety assessments	• Physical examination • Vital signs • ECG • Hematology, clinical chemistry, urinalysis • Adverse events • Immunogenicity
Other assessments	• Pharmacokinetics • Pharmacodynamics • SF-12® (to be completed by patients ≥18 years of age at Baseline) • CHQ-PF50© (to be completed by patients >5- <18 years of age at Baseline) • Sheehan Disability Scale version 3
Data analysis	Each cohort (TRAPS, HIDS, crFMF) of the study will have its own primary and secondary efficacy variables analyzed separately and independently of the other cohorts. If the primary objective is achieved, all secondary endpoints in the randomized treatment epoch (epoch 2) will be assessed in a hierarchical testing procedure to evaluate the superiority of canakinumab q4w over placebo. This is performed in order to control the overall Type I error rate ($\alpha = 0.025$, one sided tests) in the evaluation of these secondary efficacy variables. Testing is continued as long as each test showed statistical significance at the 2.5% level. The following hypotheses will be included the hierarchical testing procedure: • H_1: canakinumab q4w is not different to placebo with respect to responder rate (defined as resolution of the index flare at day 15 and no new disease flare over the 16 weeks) at Week 16. • H_2: canakinumab q4w is not different to placebo with respect to the percentage of patients with PGA < 2 at Week 16. • H_3: canakinumab q4w is not different to placebo with respect the percentage of patients with CRP ≤10 mg/L at Week 16 • H_4: canakinumab q4w is not different to placebo with respect the percentage of patients with SAA ≤10mg/L at Week 16.

	If all secondary objectives in the randomized treatment epoch are achieved, then the secondary objective in the randomized withdrawal/ dose reduction epoch (Epoch 3) will be tested. • H_5: Canakinumab q8w is not different to placebo with respect to the percentage of responders (absence of new flares) at Week 40. The 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 97.5% confidence interval will be presented. Between-treatment differences for the proportion of patients with PGA <2, CRP ≤10mg/L and SAA ≤10 mg/L at Week 16 will be analyzed using a logistic regression model with treatment group, and baseline PGA, CRP and SAA values as explanatory variables. The canakinumab treatment group will be compared to placebo with respect to the proportion of responders at Week 40 using the Fisher's exact test.
Key words	Canakinumab, interleukin-1, Hereditary Periodic Fevers, TRAPS, HIDS, crFMF, auto-inflammatory diseases

1 Introduction

1.1 Background

Hereditary Periodic Fevers (HPF), also referred to as Hereditary Recurrent Fevers or Monogenic Autoinflammatory Disorders, is a group of rare orphan diseases classified together under a single term and classically consists of 4 separate conditions: Cryopyrin Associated Periodic Syndrome (CAPS), TNF receptor Associated Periodic Syndrome (TRAPS), Hyper IgD Syndrome (HIDS) and Familial Mediterranean Fever (FMF) (Drenth et al, 2001; Goldbach-Mansky, 2012; Stojanov et al, 2005; Touitou et al, 2008). There are currently no approved treatments for TRAPS, HIDS and colchicine resistant FMF (crFMF).

A key feature of these conditions is the recurrent episodes of systemic inflammation with high and disabling fever that is accompanied by characteristic signs and symptoms of target organs and body systems (i.e. serositis, neutrophilic rash, muco-cutaneous ulcers, arthralgia/arthritis, and aseptic meningitis/headaches) (ter Haar et al, 2012; Piram et al, 2011).

The grouping of these conditions is also based on their pathophysiology, since they are now recognized as part of the expanding group of autoinflammatory disorders, which can be distinguished from autoimmune disorders by the absence of autoantibodies or antigen-specific T cells. Instead of a pathophysiology based on an adaptive immune response involving antibodies and lymphocytes, the disease mechanisms in these conditions involve innate immune regulation of cytokines and neutrophilic inflammation (Hoffmann et al, 2009).

Genome-wide association studies have begun to elucidate the molecular basis of complex autoinflammatory diseases. The discovery of disease-causing genetic variants has defined autoinflammation as a disorder within the innate immune system, implicating IL-1 as a key cytokine, and has led to a breakthrough in therapy, with IL-1 inhibitors producing rapid and sustained amelioration of symptoms (Aksentijevich and Kastner, 2011).

Canakinumab (ACZ885) is a high-affinity fully human monoclonal anti-human interleukin-1β (IL-1β) antibody of the IgG1/κ isotype. Canakinumab is designed to bind to human IL-1β blocking the interaction of this cytokine to its receptors, thus functionally neutralizing the bioactivity of this cytokine, IL-1β is recognized as one of the principal pro inflammatory cytokines in a variety of inflammatory conditions (Dinarello, 2012).

As of 30th June 2013, approximately 8’213 patients (565 of pediatric age) received ILARIS treatment in Novartis-sponsored investigational clinical trials in a wide spectrum of IL-1β driven diseases such as: Cryopyrin-associated periodic syndromes (CAPS), mild asthma, psoriasis, wet aged-related macular degeneration (AMD), gouty arthritis, type 2 diabetes mellitus, rheumatoid arthritis, and systemic juvenile idiopathic arthritis (sJIA). The post-marketing cumulative patient exposure since the first launch of the product is estimated to be approximately 2’358.4 patient-treatment-years (Investigator Brochure Edition 12.0).

Canakinumab has already been shown to be effective in treating pediatric and adult patients with 2 inherited auto-inflammatory conditions, in studies of CAPS (Lachmann et al, 2009; Kuemmerle-Deschner et al, 2011a; Kuemmerle-Deschner et al, 2011b; Kone-Paut et al, 2011)

and in more recent studies of SJIA (Ruperto et al, 2012). Both of these conditions consist of a spectrum of inherited defects and clinical syndromes, which all respond to canakinumab. In addition, canakinumab has been shown to be effective in isolated case reports and preliminary studies of HPF (Gattorno et al, 2012; Gul et al, 2012).

In over 60 countries, canakinumab has been approved in the indications of either CAPS and/ or SJIA for which inflammation and related symptoms are expected to be caused by over-production of IL-1β.

In CAPS, canakinumab (starting dose of 150 mg s.c. or 2 mg/kg every 8 weeks with the option to raise the dose up to a maximum of 600 mg or 8 mg/kg) produced a rapid and complete resolution of signs and symptoms in almost all patients, with an immediate and sustained normalization of all serological and hematological markers of inflammation. Signs and symptoms started to normalize within 1 day and more than 70% of the patients achieved a complete clinical response within 2 to 8 days, which was sustained. Response was independent of age, gender, and disease phenotype.

Over the last few years there has been an increasing body of literature about the efficacy of targeting IL-1 in a wide spectrum of auto-inflammatory conditions. In addition to isolated case reports of the efficacy of canakinumab in auto-inflammatory disorders, a preliminary demonstration of the efficacy and safety of canakinumab for the treatment of TRAPS, HIDS and crFMF has been provided by the results of 4 proof of concept (PoC), open label studies in patients with TRAPS (20 adult and pediatric patients), HIDS (9 adult and pediatric patients), and colchicine resistant/intolerant FMF (one study in 9 adults and one study in 7 pediatric patients).

In all 4 studies, using various dosing regimens, results of the primary endpoint showed rates of responses ≥85% in each of the 3 conditions with clinically meaningful improvements observed across a spectrum of measures (physician and patient based) and in inflammatory biomarkers. In addition, no new safety signals emerged in the study population.

These preliminary encouraging results warranted the further assessment of the benefit/risk of canakinumab treatment in a Phase III program in patients suffering from these 3 rare conditions.

1.2 Purpose

The purpose of this study is to determine whether canakinumab at a starting dose of 150 mg s.c. (or 2 mg/kg for patients ≤40 kg) administered every 4 weeks is able to induce and maintain a clinically meaningful reduction of disease activity after 16 weeks of treatment in a greater proportion of patients with TRAPS, HIDS, or crFMF compared to placebo. In addition, it will determine the efficacy and safety of a dose individualization (up-titration) up to a maximum of 300 mg (or 4 mg/ kg for patients ≤40 kg) every 4 weeks, in case of lack or incomplete response to the initial dosing regimen.

It is further to determine whether, in patients responding to the initial dosing regimen of every 4 weeks, canakinumab will maintain its clinical efficacy if administered at a prolonged dosing interval of 150 mg s.c. (or 2 mg/kg for patients ≤40 kg) every 8 weeks.

Data from this study are planned to support a supplemental registration of canakinumab for treatment of active TRAPS, HIDS or crFMF with a dosing regimen consistent with the exposure range approved for CAPS.

2 Study objectives

2.1 Primary objective(s)

The primary objective of the randomized treatment epoch and of the overall study is to demonstrate that canakinumab treatment at a dose of 150 mg (or 2 mg/kg in patient weighing ≤ 40 kg) s.c. every 4 weeks is superior to placebo in achieving a clinically meaningful reduction of disease activity defined as resolution of the index flare at Day 15 and no new disease flares over 16 weeks of treatment.

2.2 Secondary objectives

The secondary objectives of the study are:

- To evaluate the percentage of patients who achieve a Physician Global Assessment of Disease Activity (PGA) <2 ("minimal" or "none") 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 a clinically meaningful response (absence of new flares) when switched to canakinumab every 8 weeks compared to placebo (Epoch 3)
- To evaluate the long-term safety and tolerability and immunogenicity of canakinumab
- To evaluate the pharmacokinetics/ pharmacodynamics of canakinumab

2.3 Exploratory objectives

The exploratory objectives of the study are:

- To explore the profile in CRP and SAA over time
- To explore the PGA and Patient/ Parent's global assessment of disease activity (PPGA) profiles over time
- To explore the Physician's Severity Assessment of Disease Signs and Symptoms over time
- To explore the percentage of patients with the serologic remission defined as normalized SAA level in all patients who remain on randomized treatment or require blinded rescue over time
- To explore the percentage of patients who require blinded escape from Days 8 to 28
- To explore the number and duration of fever episodes by mean of patient diaries over time

- To explore the time to first new flare in responders in Epoch 2 switched to canakinumab every 8 weeks compared to placebo (Epoch 3)
- To evaluate the number of flares by patient and by Epoch
- To explore the use of rescue medication over time
- To explore percentage of patients who are able to reduce their corticosteroid maintenance dose at the end of each study epoch
- To explore the improvement in renal function and/ or proteinuria in patients with impaired renal function (eGFR <89 mL/min/1.73 m^2) and/ or proteinuria at Baseline
- To explore the effect of the canakinumab-induced change of disease activity levels on aspects of Health-related Quality of Life. The following questionnaires will be used:
  - Auto-Inflammatory Disease Activity Index (AIDAI)
  - SF-12 Health Survey (SF-12) *to be completed by patients ≥18 years of age at Baseline*
  - Child Health Questionnaire – Parent Form 50 (CHQ-PF50) *to be completed by patients >5 - <18 years of age at Baseline*
  - Sheehan Disability Scale version 3 (SDS v3)
- To explore the relationships between disease-associated genetic mutations and drug response
- To explore the safety and efficacy of canakinumab in the non-randomized group of Japanese crFMF patients with non-exon 10 mutations, or patients >28 days but <2 years old entering the study in the open-label arm of Epoch 2, and in the roll-over TRAPS patients previously participating in clinical study CACZ885D2203 and/or the subsequent Multiple Patient Program (MPP) treatment plan CACZ885D2207M entering the study directly in the open-label arm of Epoch 3

3 Investigational plan

3.1 Study design

Together with CAPS, the conditions of TRAPS, HIDS and crFMF are a well characterized subset within the broader family of auto-inflammatory diseases.

The rationale for an umbrella protocol enrolling patients with these 3 conditions is based upon their similarity with CAPS, and is additionally based on:

- The shared clinical features, pathophysiology, and translational evidence of the efficacy of IL-1 inhibition
- The availability of preliminary data on the efficacy and safety of canakinumab in the open-label proof of concept studies in the 3 target diseases
- The availability of safety data in patients with a spectrum of auto-inflammatory diseases (e.g. CAPS and SJIA).
- The ability to make use of the specialized, expert diagnosis/treatment centers, where pediatric and adult patients with these conditions are usually referred

This study consists of 3 cohorts (one cohort per condition: TRAPS, HIDS and crFMF), and 4 study epochs as illustrated in Figure 3-1. The cohort details of the study design are shown in Figure 3-2 and Figure 3-3. 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 Epoch 3 and the Japanese crFMF patients with non-exon 10 mutations or patients >28 days but <2 years old will enter the study in the open-label arm of Epoch 2.

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

1. A screening epoch to assess patients' eligibility of up to 12 weeks duration (Epoch 1)
2. 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:

   a. Blinded escape from Day 8 to Day 28
   b. Open-label treatment from Day 29 to Day 112

3. A randomized withdrawal epoch (Epoch 3) of 24 weeks where Canakinumab responder patients will be re-randomized to canakinumab 150 mg q8w or Placebo
4. An open-label treatment epoch (Epoch 4) of 72 weeks to collect long-term safety data for canakinumab

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:

1. A screening epoch to assess patients' eligibility of up to 12 weeks duration (Epoch 1)
2. An open-label epoch of 16 weeks (Epoch 2)
3. An open-label epoch of 24 weeks (Epoch 3)
4. An open-label treatment epoch of 72 weeks to collect long-term safety data for canakinumab (Epoch 4)

Figure 3-1 Overall study design

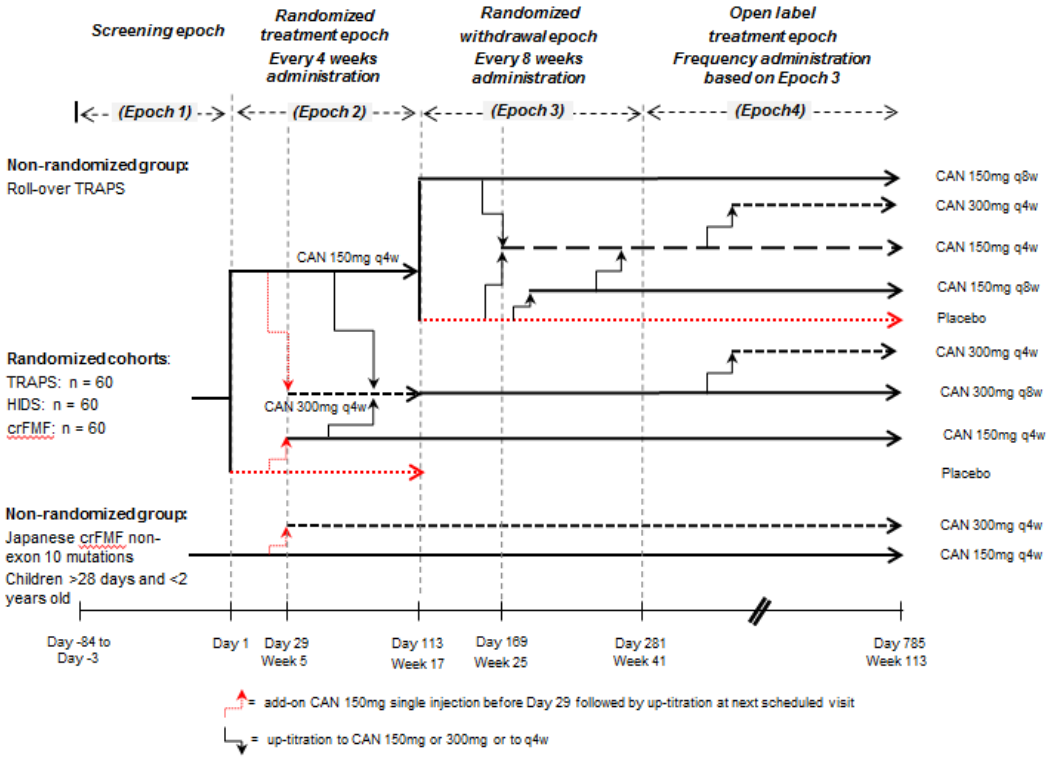


Figure 3-2 Cohort detail:
Screening (Epoch 1) and randomized treatment Epoch 2

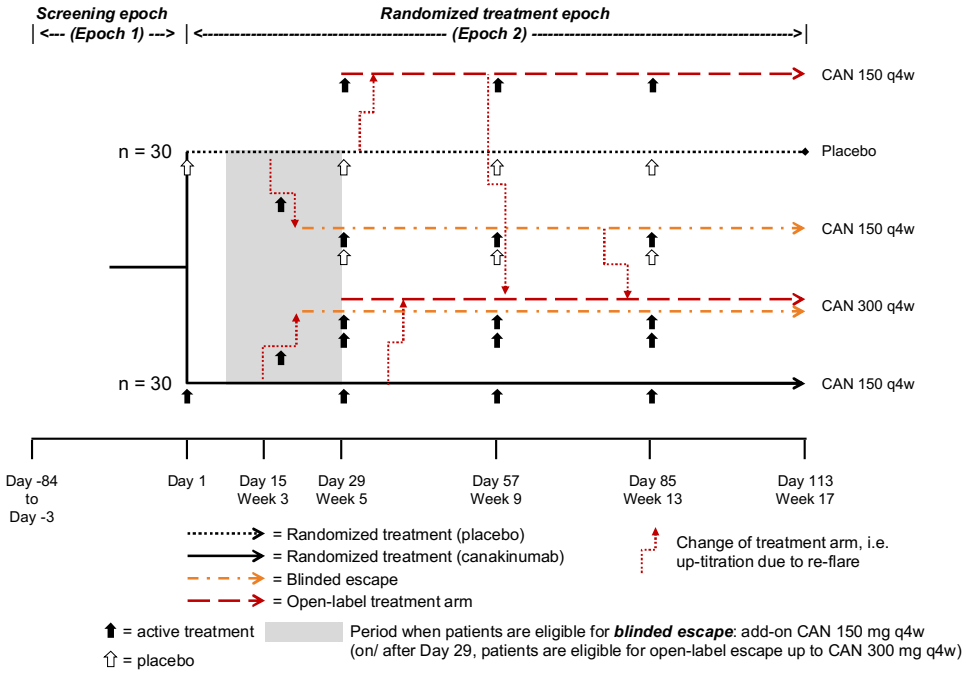
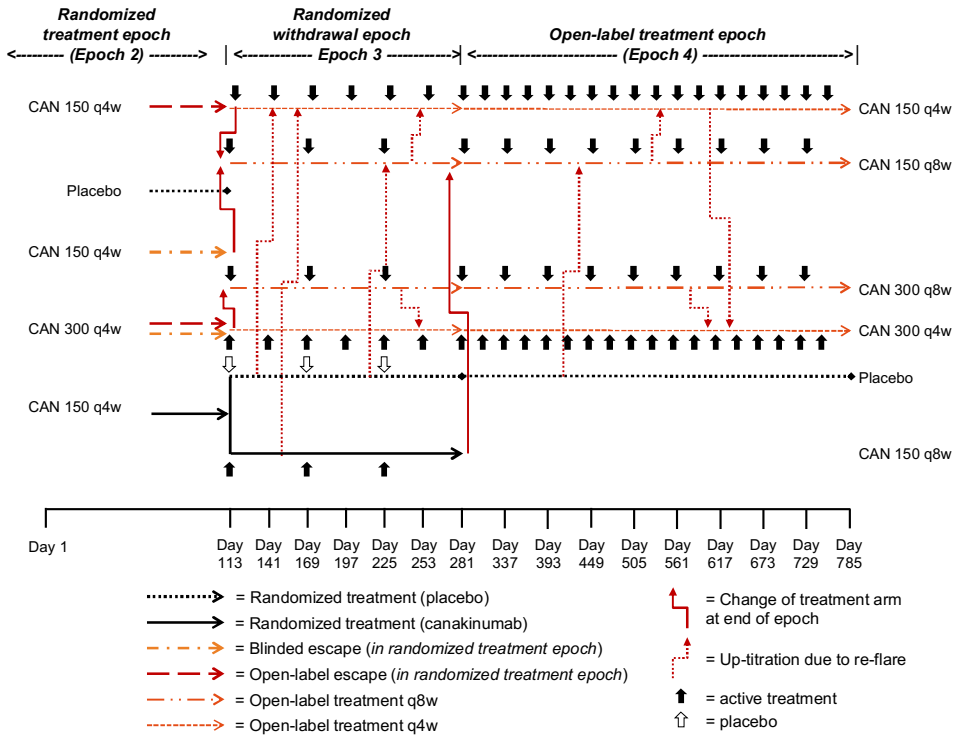


Figure 3-3 Cohort detail:
Randomized withdrawal Epoch 3 and open-label treatment Epoch 4



3.1.1 Screening epoch (Epoch 1)

A screening epoch of up to 12 weeks will be used to assess the eligibility (flare frequency/ disease activity periodicity) to one of the three study cohorts, allow patients to achieve significant biologic washout and to taper off non-allowed medications and/ or to achieve a stable regime with the permitted bridging therapies.

Patients will be asked to come fasting for screening and all subsequent visits.

At screening, the investigator will assign a patient to the respective cohort (i.e., TRAPS, HIDS or crFMF), or to the non-randomized groups, and will enter the respective condition into the IRT (Interactive Response Technology). Patients will receive a symptom diary and will be instructed to complete it and contact the site upon the first signs of a disease flare.

Patients who meet all eligibility criteria and who will show a flare during the screening epoch (Epoch 1) will be eligible to enter the randomized treatment epoch (Epoch 2). The date of onset of the flare which will result in randomization (index flare) will be entered on the eCRF.

Patients can be re-screened only once and no study-related re-screening procedure should be performed prior to written re-consent by the subject.

Mis-randomized patients are defined as cases where IRT randomization was performed 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. Mis-randomized patients will not be re-screened.

3.1.2 Randomized treatment epoch (Epoch 2)

3.1.2.1 Randomization

At baseline, eligible patients will be randomized in a ratio of 1:1 within each cohort to one of below 2 treatment arms:

- Canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) every 4 weeks (q4w)
- Placebo

Patients from the non-randomized group will enroll to the open label arm of canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) every 4 weeks (q4w). They will be eligible for add-on injection and up-titration as described in the following sections but always receive open label medication.

All patients will receive the first subcutaneous injection at Baseline and will return to the site every 4 weeks to receive additional injections of investigational treatment for 16 weeks.

The resolution of the index flare will be assessed at Day 15. Resolution of the index flare is defined as PGA <2 ("minimal" or "none"), **and** CRP within normal range (≤10 mg/L) or reduction by at least 70% from baseline. Patients whose index flare has resolved will not be up-titrated. If their index flare has not resolved by Day 15, they will be eligible for blinded escape (see Section 3.1.2.2).

Visits to assess efficacy and safety are scheduled at Day 15, Day 29 and subsequently at 4 weeks intervals during the randomized treatment epoch. Patients might receive an up-titration if they have persistent disease activity or they re-flare before Day 29 (see Section 3.1.2.2) or after Day 29 (see Section 3.1.2.3).

3.1.2.2 Blinded escape (non-resolution/ early re-flare before Day 29)

The assignment to blinded escape will be managed by the IRT.

Patients whose index flare has not resolved by Day 15 will be eligible for blinded escape.

If patients experience persistent "mild", "moderate" or "severe" disease activity (i.e., PGA ≥2 [clinical flare]), or CRP persistent >10 mg/L with less than 40% reduction from baseline from Day 8 to Day 14, they will also be eligible for blinded escape at an unscheduled visit.

In case one of the conditions described above occurs, patients will receive a single add-on s.c. injection of canakinumab (150 mg s.c. [or 2 mg/kg for patients ≤40 kg]) from Day 8 to Day 28 but will not be unblinded to their randomized treatment (see Table 3-1). This will lead to blinded up-titration to the next dosing regimen according to the initial randomized treatment and will be initiated from Day 29 onward through IRT.

- Patients randomized to canakinumab 150 mg q4w will receive 2 injections of canakinumab on Days 29, 57 and 85 equaling to a canakinumab 300 mg q4w regimen
- Patients randomized to placebo will receive 1 injection of canakinumab and 1 injection of placebo each on Days 29, 57 and 85 equaling to a canakinumab 150 mg q4w regimen

If the patient's condition is not improving after add-on injection, rescue medication should be used from Day 15 until treatment is administered at Day 29. All patients on blinded escape will be followed-up for efficacy and safety.

Non-randomized cohort

Canakinumab naïve Japanese crFMF patients with non-exon 10 mutations or patients >28 days but <2 years old will initiate open-label treatment receiving canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q4w at Day 1. Index flare resolution will be assessed at Day 15.

Patients experiencing persistent "mild", "moderate" or "severe" disease activity (i.e., PGA ≥2 [clinical flare]), or CRP persistent >10 mg/L with less than 40% reduction from baseline from Day 8 to Day 28 can receive a single add-on s.c. injection of canakinumab (150 mg s.c. [or 2 mg/kg for patients ≤40 kg]). If the patient's condition is not improving after add-on injection, rescue medication should be used until the patient's next visit at Day 29 when study treatment will be administered.

In case of add-on injection, up-titration to canakinumab of 300 mg (or 4 mg/ kg for patients weighing ≤40 kg) q4w will be initiated from Day 29 onward through IRT. Those patients will not be eligible for any further up-titration but may stay in the study receiving canakinumab of 300 mg (or 4 mg/ kg for patients weighing ≤40 kg) q4w if they are considered partial responders by the investigator.

All patients in open label arm will be followed-up for efficacy and safety.

3.1.2.3 Open label treatment arm (re-flare on/ after Day 29)

If on Day 29 or after Day 29, patients still have "mild", "moderate" or "severe" disease activity (PGA ≥2 [clinical flare] and CRP ≥30 mg/L [serological flare]), up-titration to the next dosing regimen is allowed and patients will initiate open label escape at the next scheduled visit including Day 29 (see Table 3-1).

The following up-titration will be initiated at the next scheduled visit based on the IRT information:

- Patients randomized to placebo will receive canakinumab 150 mg q4w. If they still have "mild", "moderate" or "severe" disease activity (PGA ≥2 [clinical flare] and CRP ≥30 mg/L [serological flare]) or re-flare at the next scheduled visit, they will increase the dose to canakinumab 300 mg q4w
- Patients randomized to canakinumab 150 mg q4w will increase the dose to canakinumab 300 mg (or 4 mg/ kg for patients weighing ≤40 kg) q4w

Table 3-1 Criteria for add-on injection or up-titration in Epoch 2

	PGA criteria	CRP criteria	Treatment option	IRT update
Day 8 to 14	Persistent PGA ≥2 **OR**	CRP persistent >10 mg/L with less than 40% reduction from baseline	Add-on injection allowed	Blinded up-titration effective at next scheduled visit (Day 29)
Day 15	PGA ≥2 **OR**	CRP >10 mg/L and no reduction by at least 70% from baseline	No Index flare resolution* Add-on injection allowed (only if add-on injection was not received earlier)	Blinded up-titration effective at next scheduled visit
Day 16 to 28	PGA ≥2 **OR**	CRP >10 mg/L and no reduction by at least 70% from baseline	Add-on injection allowed (only if add-on injection was not received earlier)	Blinded up-titration effective at next scheduled visit
Day 29 to 112	PGA ≥2 **AND**	CRP ≥30mg/L	Up-titration allowed	Open label up-titration effective at next scheduled visit including Day 29 visit

* For patient with index flare resolution at Day 15, criteria defined for Day 29 will be applied
Single Add-on injection is allowed only once in Epoch 2

For patients who already received blinded escape prior to Day 29 and require a second up-titration:

- Patients randomized to placebo *who received blinded escape* (150 mg q4w) *prior to Day 29* will receive open-label canakinumab 300 mg q4w
- Patients randomized to canakinumab 150 mg q4w *who received blinded escape* (add on 150 mg q4w) *prior to Day 29* must not further up-titrate

Patients who are on the highest allowed dose of canakinumab of 300 mg (or 4 mg/ kg for patients weighing ≤40 kg) q4w and re-flare (PGA ≥2 **and** CRP ≥30 mg/L) will not be eligible for any further up-titration but may stay in the study receiving canakinumab of 300 mg (or 4 mg/ kg for patients weighing ≤40 kg) q4w if they are considered partial responders by the investigator. If these patients discontinue treatment with canakinumab, they should remain in the study for safety follow-up.

All patients on the open-label treatment arm will be followed-up for safety.

3.1.3 Randomized withdrawal epoch (Epoch 3)

3.1.3.1 Re-randomization

All patients randomized to placebo at baseline and completing the randomized treatment epoch (Epoch 2) without any re-flare will be considered placebo-responders. To avoid exposure to canakinumab which may not be justified in light of the clinical status, these patients will be withdrawn from the study treatment.

Patients who initiated blinded escape or entered the open-label treatment arm in the randomized treatment epoch (Epoch 2), non-randomized cohort patients and roll-over TRAPS patients will not be re-randomized and will enter the open-label treatment arm in Epoch 3; for patient management details refer to Section 3.1.3.2.

All patients randomized to canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q4w at baseline and completing the randomized treatment epoch (Epoch 2) who did not require blinded escape or to enter the open-label treatment arm will be re-randomized in a ratio of 1:1 to:

- Canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q8w
- Placebo

Re-randomized patients will receive the first s.c. injection on Day 113 and will return to the site every 8 weeks to receive additional injections of investigational treatment for 24 weeks.

Visits to assess efficacy and safety are scheduled at 8 weeks intervals during the randomized withdrawal epoch (Epoch 3). Patients might receive an up-titration if they re-flare at unscheduled visits (see Section 3.1.3.2).

3.1.3.2 Open-label treatment arm

The following additional up-titration (open-label treatment arm) will be allowed and managed by the IRT:

- Patients re-randomized to placebo who re-flare within an interval of less than 8 weeks will switch to open-label canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q4w
- Patients re-randomized to placebo who re-flare within an interval of more than 8 weeks will switch to open-label canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q8w

- Patients re-randomized to canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q8w will revert back to canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q4w in case of a re-flare

Non responders and non-randomized cohort patients

Non responders (patients who initiated blinded escape or entered the open-label treatment arm in the randomized treatment epoch (Epoch 2)) and non-randomized patients will be switched to a q8w dosing interval (keeping their current escape dose [150 mg or 300 mg]). Patients will be allowed to revert back to q4w in case of a re-flare.

Roll-over TRAPS patients

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 at Day 113 (Epoch 3) in the open-label treatment arm and continue receiving canakinumab based on their current dosing regimen either 150 mg or 300 mg (2 mg/kg or 4 mg/kg for patients weighing ≤40 kg) q8w. These patients need to be screened (Day 1 assessments to be performed) before being eligible for entering Epoch 3 at Day 113. In case of experiencing a flare, up-titration will be allowed as specified above in this section.

3.1.4 Open-label treatment epoch (Epoch 4)

All patients who were re-randomized to placebo on Day 113 but completed the randomized withdrawal epoch (Epoch 3) without re-flare will enter Epoch 4. They will present for scheduled visits but will not receive any investigational drug. In case they re-flare, they will enter the open-label treatment arm receiving canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q8w. In case of experiencing a flare, up-titration will be allowed as specified in Section 3.1.3.2.

All other patients will enter the long-term safety open-label treatment epoch of 72 weeks duration. They will continue on their last dosing regimen as administered during the randomized withdrawal epoch (Epoch 3). Visits to assess efficacy and safety are scheduled at 8 weeks intervals during the open-label treatment epoch (Epoch 4).

In case of re-flares (PGA ≥2 and CRP ≥30 mg/L) before the next scheduled visit, (step-wise) up-titration up to a dosing regimen of canakinumab 300 mg (or 4 mg/kg for patients weighing ≤40 kg) q4w will be allowed. The same principles for up-titration as outlined in Section 3.1.2.3 or Section 3.1.3.2 will apply.

No down-titration will be allowed during Epoch 4.

Visits to assess efficacy and safety are scheduled at 8 weeks intervals during the open-label treatment epoch (Epoch 4). Patients might receive an up-titration if they re-flare during Epoch 4 Patients up-titrated to q4w administration will come back every 4 weeks for unscheduled visits at Day 309, Day 365, Day 421, Day 477, Day 533, Day 589, Day 645, Day 701 and Day 757 in addition to the visits scheduled defined in Table 6-2.

3.2 Rationale of study design

This study design is customized to this orphan disease area, while the development programs conducted so far in similar conditions (i.e., CAPS, SJIA) have been based mostly on open-label single arm studies and studies with an open-label run-in followed by a randomized withdrawal/ dosing frequency reduction.

One pertinent recent precedence for a placebo controlled randomized parallel group study in auto-inflammatory diseases is represented by the tocilizumab registration trial in SJIA (De Benedetti et al., 2012).

This study design with its escape options during the randomized treatment epoch (Epoch 2) might provide limited placebo controlled safety data whereas the randomized withdrawal/ dose reduction epoch (Epoch 3) will assess the potential of maintaining clinical efficacy at a reduced dosing frequency. The open-label treatment epoch (Epoch 4) will provide long-term safety data.

However, safety data will be evaluated open-label within individual cohorts as well as at pooled level.

3.3 Rationale of dose/ regimen, route of administration and duration of treatment

The initial dosing regimen defined for this protocol (150 mg s.c. or 2 mg/ kg s.c.) is based on the evidence from the clinical program in approved indications such as CAPS and the completed or ongoing trials in TRAPS, HIDS, and crFMF in light of the shared IL-1 beta-driven pathophysiology of the disease.

Because of the rarity of these three conditions no formal dose finding study was conducted and the dosing regimens tested in the open-label studies were derived from the investigators' translational experience with other IL-1 inhibitors used off-label and for which usually higher doses compared to those used in CAPS were needed to achieve control of disease activity in HPF.

A dosing schedule of 150 mg s.c. every 4 weeks (or 2 mg/kg s.c every 4 weeks for patients ≤40 kg) has been demonstrated to be highly effective in three (of the four) open-label PoC trials, specifically those in TRAPS and crFMF patients. A higher dose (300 mg or 4 mg/kg) with a longer interval (every 6 weeks) was tested in HIDS patients and was very effective.

In this study, an initial dose regimen of 150 mg s.c. (or 2 mg/kg s.c for patients ≤40kg) q4w is used to harmonize exposure between these three conditions while allowing for up-titration to a maximal dose of canakinumab 300 mg (or 4 mg/kg for patients weighing ≤40 kg) q4w to optimize the regimen and thus achieve efficacy in difficult cases.

In order to evaluate if clinical efficacy can be maintained at a lower dosing frequency, canakinumab 150 mg s.c. (or 2 mg/kg s.c for patients ≤40 kg) at a reduced frequency (q8w) will be evaluated during the randomized withdrawal epoch (Epoch 3).

The dose regimens to be used in the open-label treatment arm (across Epochs 2 – 4) are considered to constitute the lowest clinically efficacious doses to maintain clinical efficacy in individual patients.

Of note, the safety profile of canakinumab in CAPS patients has not been observed to change with up-titration to 300 mg (or 4 mg/kg s.c. for patients ≤40 kg) every 8 weeks. The safety of canakinumab is supported by clinical and post-marketing safety data from CAPS using doses up to 600 mg (or 8 mg/kg) every 8 weeks and from SJIA clinical trials which utilized higher starting doses of 4 mg/kg every 4 weeks. Safety data from all four of the open label PoC trials in TRAPS, HIDS and crFMF are consistent with the known safety profile of canakinumab.

The protocol will include patients as young as 2 years old in the randomized population and >28 days but <2 years old in the non-randomized group, while the current trials had a minimum age of 4 years. The CAPS experience suggests that patients less than 4 years old (<15 kg of weight) often require higher starting doses (4 mg/kg q8w), likely related to their relatively higher levels of IL-1β and higher relative prevalence of the more severe phenotype. This protocol will use the same 2 mg/kg s.c. dose in pediatric patients <4 years of age (or <15 kg of body weight), with the possibility of up-titration based on early assessment of clinical response. In CAPS patients up-titration in patients weighing ≤40 kg, is associated with transient, non-serious infections common in children (e.g., ear infections, gastroenteritis). The same patients did not experience increasing serious infections or hematology abnormalities with dose escalations.

In summary, an initial dose of 150 mg s.c. (or 2 mg/kg s.c. for patients ≤40 kg) q4w is expected to provide positive benefit /risk to TRAPS, HIDS or crFMF patients participating in this trial by providing exposure to canakinumab which has shown evidence of efficacy in prior open label trials and which is often necessary in pediatric patients or in more severe clinical phenotypes. The resulting range of exposure is regarded as safe, as previously demonstrated in CAPS patients and as observed in the safety profile of patients participating in the preliminary studies.

3.4 Rationale for choice of comparator

Currently there are no approved treatment options for the target patient population. Therefore there are no ethical concerns with using a placebo comparator, which will provide a good estimate of the size of the treatment effect. Thus the use of a placebo comparator with an early escape option is appropriate.

3.5 Purpose and timing of interim analyses/design adaptations

If enrollment into the study is completed as scheduled, no interim analysis of the randomized treatment epoch (Epoch 2) is planned (see Section 9.6 for details about scenarios which may trigger an interim analysis).

Interim analyses at the end of Epoch 2 and Epoch 3 to support regulatory filing will be performed as detailed in Section 9.6.

3.6 Risks and benefits

In TRAPS, HIDS and FMF, antipyretics, such as NSAIDs and paracetamol, often have some effect at reducing fever and associated symptoms, but they do not prevent or change the course of flare (ter Haar et al, 2012; Hoffman, 2009). Regular, repeated dosing is often required for the duration of the episode, which raises concern for the occurrence of adverse effects, including gastrointestinal irritation or liver toxicity.

For the past 30 years, maintenance-dose colchicine has been the mainstay of therapy for preventing attacks and substantially reducing the risk of amyloidosis in patients with FMF. Occasionally, compliance can be affected by the gastrointestinal adverse effects that are sometimes associated with increasing the colchicine dose. There are rare patients (in the range of 5-10%) with FMF who are considered to be colchicine resistant (incomplete response to adequate colchicine dosing). However, colchicine is less effective in TRAPS and HIDS.

Corticosteroids have limited clinical efficacy in most of the recurrent febrile syndromes, with reports of very high doses being required to achieve any benefit.

Thus the risks are associated with the use of high doses of antipyretics, colchicine and corticosteroids, which offer only symptomatic relief, without sustained benefit.

Preliminary data from the 4 small pilot studies with canakinumab in these 3 indications both in adult and pediatric patients, as well as the ongoing worldwide pharmacovigilance activities have not identified any new safety signals specific for patients with TRAPS, HIDS, crFMF in patients treated with canakinumab.

The risk to subjects in this trial will be minimized by compliance with the inclusion/ exclusion criteria, close clinical and laboratory monitoring, adherence to the protocol guidelines for dose administration/escape treatment rules and implementation of a Risk Management Plan in place for canakinumab.

Canakinumab is known to be highly effective and safe in children and adults with CAPS, a spectrum of inherited auto-inflammatory syndromes that are similar to TRAPS, HIDS and crFMF. Preliminary data from the 4 PoC open-label trials with canakinumab in these 3 indications in both in adult and pediatric patients has shown canakinumab to be effective, and potentially able to treat the underlying inflammation, rather than just the disease symptoms.

4 Population

The study population will consist of male and female patients >28 days and confirmed TRAPS (cohort 1), HIDS (cohort 2), or crFMF (cohort 3).

It is aimed to randomize a total of 180 patients (60 per cohort, 30 per treatment arm) in approximately >20 centers worldwide. Since a 20% screening failure rate is expected, it is estimated that approximately 225 patients have to be screened.

The following patient populations will be screened at Day 1 and directly entered into the open-label treatment arm of the randomized withdrawal epoch (Epoch 3) at Day 113:

- TRAPS patients previously participating in clinical study CACZ885D2203 or the subsequent MPP treatment plan CACZ885D2207M (at most 19 patients).

In addition, the following patient populations will be screened and will enter into the open-label treatment arm of the Epoch 2 at Day 1:

- Male and female patients >28 days but <2 years old with bodyweight ≥3.75 kg
- Approximately 5 Japanese crFMF patients with non-exon 10 mutations otherwise fulfilling all the mandatory inclusion and exclusion criteria.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

4.1.1 Criteria applicable for all cohorts

1. Patient's written informed consent from those ≥18 years of age must be obtained before any assessment is performed. Parent or legal guardian's written informed consent and child's assent, if appropriate, are required before any assessment is performed for patients < 18 years of age.
2. Male and female patients at least 2 years of age at the time of the screening visit. Male and female patients >28 days but <2 years old with bodyweight ≥3.75 kg at the time of the screening visit will be enrolled in the open label arm only.

4.1.2 Criteria applicable for patients with TRAPS (cohort 1)

At Screening:

3. Clinical diagnosis of TRAPS but no active flare at the time of screening
4. Mutation of the TNFRSF1A gene
5. Chronic or recurrent disease activity periodicity. Recurrent TRAPS patients must have experienced more than 6 flares/ year.
   For patients receiving therapy with biologics, this criterion applies to the last 12 months before they started any therapy with biologics.

At Randomization:

6. Active clinical TRAPS flare as evidenced by "mild", "moderate" or "severe" disease activity (PGA ≥2)
7. CRP >10 mg/L (Normal CRP range ≤10 mg/L)

At beginning of randomized withdrawal epoch (Epoch 3) (applicable only for patients previously participating in CACZ885D2203 or CACZ885D2207M):

8. Completion of clinical study CACZ885D2203 and/or
9. Current participation in MPP treatment plan CACZ885D2207M on a stable dose regimen

4.1.3 Criteria applicable for patients with HIDS (cohort 2)

At Screening:

10. Clinical diagnosis of HIDS but no active flare at the time of screening

11. Genetic/enzymatic diagnosis of HIDS
12. Prior documented history of ≥3 febrile acute HIDS flares in a 6-month period when not receiving prophylactic treatment (e.g. daily anakinra treatment).
    For patients receiving therapy with biologics, this criterion applies to the last 12 months before they started any therapy with biologics.

At Randomization:

13. Active clinical HIDS flare as evidenced by "mild", "moderate" or "severe" disease activity" (PGA ≥2)
14. CRP >10 mg/L (Normal CRP range ≤10 mg/L)

4.1.4 Criteria applicable for patients with crFMF (cohort 3)

At Screening:

15. Diagnosis of type 1 FMF disease according to Tel Hashomer criteria (Livneh et al, 1997) but no active flare at the time of screening
16. At least one of the known MEFV gene exon 10 mutations
17. One of the following two:
    a. Documented active disease despite colchicine therapy (from a minimum of 1.5 mg up to 3.0 mg/day or equivalent pediatric age/ weight adjusted dosing regimen depending on Local Guidelines/ standard practice). Patients on current colchicine treatment will continue at stable dose during the study.
    b. Documented intolerance to effective doses of colchicine (from a minimum of 1.5 mg up to 3.0 mg/day or equivalent pediatric age/ weight adjusted dosing regimen depending on Local Guidelines/ standard practice)
18. Historical data showing a frequency of at least 1 attack/month
    For patients receiving therapy with biologics, this criterion applies to the last 12 months before they started any therapy with biologics.

At Randomization:

19. Acute crFMF flare characterized by inflammation and serositis in the opinion of the investigator, lasting approximately 12 to 72 hours
20. Active clinical crFMF flare as evidenced by "mild", "moderate" or "severe" disease activity" (PGA ≥2)
21. CRP >10 mg/L (Normal CRP range ≤10 mg/L)

Applicable exclusively for Japanese crFMF patients with non-exon 10 mutations:

At Screening:

22. Criteria #15, #17, #18 as outlined above
23. At least one MEFV gene non-exon 10 mutation

At beginning of Epoch 3:

24. Criteria #19, #20, and #21 as outlined above

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Use of the following therapies:
   a. Corticosteroids (prednisone equivalent > 0.2 mg/kg/day [or greater than the maximum of 15 mg/ day for children over 60 kg]) within 1 week prior to Baseline
   b. Anakinra within 24 hours prior to Baseline
   c. Canakinumab within 3 months prior to Baseline (*not applicable for patients rolling-over from CACZ885D2203/ CACZ885D2207M)*
   d. Rilonacept within 4 weeks prior to Baseline
   e. Tocilizumab within 6 weeks prior to Baseline
   f. Etanercept within 2 weeks prior to Baseline
   g. Infliximab within 4 weeks prior to Baseline
   h. Adalimumab within 6 weeks prior to Baseline
   i. Golimumab within 6 weeks prior to Baseline
   j. Certolizumab within 6 weeks prior to Baseline
   k. Abatacept within 7 weeks prior to Baseline
   l. Tofacitinib within 24 hours prior to Baseline
   m. Rituximab within 24 weeks prior to the Baseline
   n. Leflunomide within 8 weeks prior to the Baseline
      Documentation of a completion of a full cholestyramine elimination treatment after most recent leflunomide use will be required.
   o. Thalidomide within 4 weeks prior to Baseline
   p. Cyclosporine within 4 weeks prior to Baseline
   q. Intravenous immunoglobulin (i.v. Ig) within 8 weeks prior to Baseline
   r. 6-Merceptopurine, azathioprine, cyclophosphamide, or chlorambucil within 12 weeks prior to Baseline
   s. Intra-articular, peri-articular or intramuscular corticosteroid injections within 4 weeks prior to Baseline
   t. Any other investigational biologics within 3 half-lives prior to the Baseline visit
   u. Any other investigational drugs, other than investigational biologic treatment, within 30 days (or 3 months for monoclonal antibodies) or 3 half-lives prior to the Baseline visit, whichever is longer
2. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes or to any of the excipients.
3. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:

   a. Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
   b. History of familial long QT syndrome or known family history of Torsades de Pointes
4. Concomitant use of agents known to prolong the QT interval unless it can be permanently discontinued for the duration of the study
5. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
6. Significant medical diseases, including but not limited to the following:
   a. Any organ transplant recipient, or patient currently listed for imminent transplant (*i.e. patients on an administrative transplant waiting list will not be excluded*), or admitted for any transplantation.
   b. Elevated alanine aminotransferase (ALT) ≥3x ULN (*if ALT at screening is >3x but <5x ULN, a re-test will be allowed. If ALT at re-test is <3x ULN and confirmed at another re-test, the patient will be eligible for participation*)
   c. Elevated aspartate aminotransferase (AST) ≥3x ULN (*if AST at screening is >3x but <5x ULN, a re-test will be allowed. If AST at re-test is <3x ULN and confirmed at another re-test, the patient will be eligible for participation*)
   d. Increase in total bilirubin (TBL) defined as per CTC Grade ≥2: TBL >1.5x ULN
   e. Serious hepatic disorder (Child-Turcott-Pugh scores B or C)
   f. Chronic Kidney Disease as per NKF stages ≥4: eGFR ≤29 mL/min/1.73 m^2
   g. Thyroid disease (unless the patient is taking a stable dose of thyroid hormone or anti-thyroid medications [hyperthyroidism] for at least 12 weeks), which in the opinion of the investigator should exclude the patient from the study
   h. Diagnosis of active peptic ulcer disease as determined by endoscopy, radiography, angiography, or other appropriate means within 12 months prior to screening.
   i. Coagulopathy (*regardless if controlled by pharmacotherapy or not*)
   j. Significant CNS effects including vertigo and dizziness, or major neurologic event, including cerebrovascular events, within 60 days of screening
7. Any conditions or significant medical problems which in the opinion of the investigator immunocompromises the patient and/ or places the patient at unacceptable risk for immunomodulatory therapy, such as:
   a. Absolute neutrophil count (ANC) decreased as per CTC Grade ≥1: Neutrophils <LLN – 1.5 x 10^9/L or below
   b. Thrombocytopenia as per CTC Grade ≥1: Platelets <LLN – 75.0 x 10^9/L or below
   c. Any active or recurrent bacterial, fungal (with exception of onychomycosis) or viral infection
   d. Presence of Human Immunodeficiency Virus (HIV) infection, Hepatitis B or Hepatitis C infections based on screening lab results
   e. Clinical evidence or history of multiple sclerosis or other demyelinating diseases, or Felty's syndrome

8. History or evidence of tuberculosis (TB) (active or latent) infection or one of the risk factors TB such as but not limited or exclusive to:
   a. History of any of the following: residence in a congregate setting (e.g. jail or prison, homeless shelter, or chronic care facility), substance abuse (e.g. injection or non-injection); health-care workers with unprotected exposure to patients who are at high risk of TB or patients with TB disease before the identification and correct airborne precautions of the patient, or
   b. Close contact (i.e. share the same air space in a household or other enclosed environment for a prolonged period (days or weeks, not minutes or hours)) with a person with active pulmonary TB disease within the last year, or
   c. Evidence of TB infection (active or latent) determined by positive QuantiFERON (QFT-TB G In-Tube) test or positive Purified Protein Derivative (PPD) test (≥5 mm induration) at screening or within 2 months prior to the screening visit, according to the national guidelines. If presence of TB infection (active or latent) is established then treatment for TB as per national guidelines must have been initiated or completed prior to randomization. In the absence of national guidelines, the following has been demonstrated: TB has been treated adequately by antibiotics, cure can be demonstrated and risk factors resulting in TB exposure and contracting have been removed.
9. Administration of any investigational drug or implantation of investigational device, or participation in another trial, within 30 days before screening (*not applicable for patients rolling-over from CACZ885D2203/ CACZ885D2207M).*
10. Live vaccinations within 3 months prior to the start of the trial, during the trial, and up to 3 months following the last dose
11. Donation or loss of blood (amount depending on age and weight, 10-20% or more of volume, within 8 weeks prior to first dosing, or longer if required by local regulation
12. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
13. Female adolescents (≤18 years of age) of childbearing potential who do not agree to abstinence or, if sexually active, do not agree to the use of contraception as defined in the exclusion criterion for women of child bearing potential. For further information, please refer to Section 6.5.6.
14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment. Effective contraception methods include:
   a. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
   b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

c. Male sterilization (at least 6 m prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
d. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
e. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
f. Placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception women should have been stabile on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Novartis will provide the following investigational treatment:

1. Canakinumab solution for injection in vial which contains 150 mg/mL canakinumab in 1 mL solution
2. Placebo matching the canakinumab solution.

5.1.2 Additional study treatment

No additional treatment beyond investigational treatment is requested for this trial.

5.2 Treatment arms

In the randomized treatment epoch (Epoch 2), patients in each cohort will be assigned to one of the following 2 treatment arms in a ratio of 1:1 at Baseline:

1. Canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q4w
2. Placebo

Patients who will be eligible for blinded escape (see Section 3.1.2.2) will receive a single add-on injection of canakinumab (150 mg [or 2 mg/kg for patients weighing ≤40 kg]) from Day 8 to Day 28. Patients will then receive below treatment until investigational treatment discontinuation (TD)/ premature subject withdrawal (PSW):

1. Patients randomized to canakinumab 150 mg q4w will switch to canakinumab 300 mg (or 4 mg/kg for patients weighing ≤40 kg) q4w
2. Patients randomized to placebo switch to canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q4w

Patients who require additional up-titration (open-label treatment arm as detailed in Section 3.1.2.3) will switch to canakinumab 300 mg s.c. (or 4 mg/ kg for patients weighing ≤40 kg) q4w.

In the randomized withdrawal epoch (Epoch 3), responders to canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q4w (see Section 3.1.3 for details) will be re-randomized on Day 113 in a ratio of 1:1 to:

1. Canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q8w
2. Placebo

Patients who required up-titration during Epoch 2 will start their participation in Epoch 3 in the open-label treatment arm (canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q8w or canakinumab 300 mg (or 4 mg/kg for patients weighing ≤40 kg) q8w. Any up-titration in case of lack of therapeutic effect will be allowed as outlined in Section 3.1.3.2.

Patients from the non-randomized group (patients >28 days but <2 years old) and Japanese crFMF patients with non-exon 10 mutations) entering the study at Epoch 2 will receive open-label canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q4w.

TRAPS patients previously participating in CACZ885D2203 or CACZ885D2207M entering the study at the beginning of Epoch 3 will be assigned to the open-label treatment arm at a dose of canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q8w or canakinumab 300 mg (or 4 mg/kg for patients weighing ≤40 kg) q8w.

Open-label treatment in Epoch 4 will be handled as detailed in Section 3.1.4.

5.3 Treatment assignment, randomization

At Baseline, all eligible patients within each cohort will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/ her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/ exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

At the beginning of the randomized withdrawal epoch (Epoch 3), all eligible patients within each cohort will be re-randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/ her delegate will contact the IRT after confirming that the patient qualifies for entering the withdrawal epoch.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that

automates the random assignment of patient numbers to randomization numbers. [redacted]

Randomization will be stratified by disease cohort.

[redacted]

Patients from the non-randomized cohort and roll-over TRAPS patients will be assigned to the open-label treatment in Epoch 2 and Epoch 3 respectively via IRT.

In case of add-on injection from Day 8 to Day 28, IRT will assign a unique medication number for blinded administration. At the next scheduled visit, the new dosing regimen will be initiated by IRT automatically and medication number assigned accordingly.

In case of up-titration from Day 29 onwards, the new dosing regimen will be initiated by IRT automatically at the next scheduled visit (including Day 29 visit) and medication number assigned accordingly.

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the randomized or re-randomized treatment assignment from the time of randomization until database lock, using the following methods:

1. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:
   a. Unblinded lab personnel charged with conducting the PD/ PK and/ or IG assays.
2. The identity of the treatments will be concealed by the use of investigational treatment that are all identical in packaging, labeling, schedule of administration, appearance.

Unblinding will only occur for placebo responders at the end of the randomized treatment epoch (Epoch 2), in the case of patient emergencies (see Section 5.5.12), in case of an interim analysis (see Section 9.6) and at the conclusion of the study.

The randomization codes associated with patients from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until data base lock.

5.5 Treating the patient

5.5.1 Patient numbering

[redacted] Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site should select the CRF book with a matching Subject Number from the EDC system to enter data.

The previous Subject-ID of TRAPS patients previously participating in CACZ885D2203 or CACZ885D2207M will be collected in the CRF.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered into the respective electronic CRF page.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with investigational treatment in packaging of identical appearance.

The investigational treatment packaging/ kit has a 2-part label. A unique medication number is printed on each part of this label. The kit(s) dispensed will be the appropriate drug and quantity appropriate to the respective treatment arm and dose level. Investigator staff will identify the investigational treatment package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused investigational treatment and packaging at the end of the study or at the time of discontinuation of investigational treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational treatment, packaging, drug labels, and a

copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of other investigational treatment

Not applicable.

5.5.4 Instructions for prescribing and taking investigational treatment

The s.c. injections of investigational treatment may be administered into the patient's arm or thigh. Detailed instructions on the preparation and administration of the study drugs will be described in the Pharmacist Manual and provided to each site.

All patients will receive a first single s.c. injection of investigational treatment at Baseline. Following Baseline, patients will receive injections every 4 weeks until Day 113. Those patients who will be eligible for blinded escape (Section 3.1.2.2) will receive an additional s.c. injection of investigational drug between Day 8 and Day 28.

Depending on a patient's treatment assignment, i.e. blinded escape, or open-label treatment arm, patients will receive 1 or 2 injections per visit.

Patients, who will be eligible for randomized withdrawal in Epoch 3, will receive injections every 8 weeks till Day 281.

Patients in the open-label treatment arm (Epoch 2, Epoch 3 and or Epoch 4) will receive 1 or 2 injections every 4 or 8 weeks, depending upon individual need until TD/ PSW.

A graphical layout of the patient flow and administration of individual investigational treatment doses is shown in Figure 3-2 and Figure 3-3. Details about the doses administered are also described in Section 5.2.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

All kits of investigational treatment assigned by the IRT will be recorded/ databased in the IRT.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Any other investigational treatment dose adjustments than detailed in Section 3.1.2 (Epoch 2), Section 3.1.3 (Epoch 3) or Section 3.1.4 (Epoch 4) and/ or interruptions are not permitted.

5.5.6 Rescue medication

Increase of corticosteroid maintenance dose or intermittent steroid treatment up to the dose detailed in Table 5-1 may be used as rescue therapy.

Standard doses of NSAIDs can be used from Day 15 inclusive on an as needed basis to treat the sign and symptoms of TRAPS, HIDS or crFMF during acute flares at the discretion of the investigator. Before Day 15, NSAIDs should not be used for treating any signs or symptoms of the index flare.

Use of rescue medication must be recorded on the concomitant medications page in the CRF.

5.5.7 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded.

5.5.8 Prohibited Treatment

Use of the treatments displayed in Table 5-1 is NOT allowed after Screening.

Table 5-1 Prohibited treatment

Medication	Action to be taken
Corticosteroid maintenance (prednisone equivalent > 0.2 mg/ kg/ day or greater than the maximum of 15 mg/ day for children over 60 kg).	Investigational treatment does not need to be discontinued as a result of this protocol deviation (PD)
Anakinra	Investigational treatment to be discontinued[2]
Rilonacept, tocilizumab, rituximab and any other biologics[1] (investigational or marketed)	Investigational treatment to be discontinued[2]
Etanercept, adalimumab, infliximab, or any TNF inhibitor (investigational or marketed)	Investigational treatment to be discontinued[2]
Leflunomide, thalidomide, cyclosporine, or i.v. Ig	Investigational treatment to be discontinued[2]
Tofacitinib	Investigational treatment to be discontinued[2]
6-Merceptopurine, azathioprine, cyclophosphamide, or chlorambucil	Investigational treatment to be discontinued[2]
Intra-articular, peri-articular or intramuscular corticosteroid injections	Investigational treatment to be discontinued[2]
Any other investigational non-biological drug	Investigational treatment to be discontinued[2]
Any live vaccination[1]	Investigational treatment to be discontinued[2]
Treatment for tuberculosis	Investigational treatment to be discontinued

[1] It is recommended not to initiate any live vaccination or biologic treatment until 3 months after the last dose of investigational treatment. Killed or inactivated vaccines may be permitted according to the investigator's discretion.

[2] Investigational treatments must be permanently discontinued but patient will remain in the study and will be followed-up for safety.

5.5.9 Discontinuation of study treatment

Patients may voluntarily discontinue investigational treatment for any reason at any time.

The investigator should discontinue investigational treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Investigational treatment must be discontinued under the following circumstances:

- Emergence of the following adverse events:
  a. Absolute QTcF > 500 msec, confirmed by repeat ECG measurements

b. Serious infections combined with neutropenia CTC grades ≥1 (ANC <2.0 x 10^9/L)
c. CKD as per NKF stages ≥4: eGFR ≤29 mL/min/1.73 m^2
d. Confirmed diagnosis of latent or active TB
e. Onset of any malignancy

- Any of the following laboratory abnormalities:
  a. Neutropenia CTC Grades ≥2 : ANC <1.5 x 109/L
  b. Thrombocytopenia CTC Grade 4: Platelets <10.0 x 109/L
- Pregnancy
- Use of prohibited treatment as per Table 5-1
- Any other protocol deviation that results in a significant risk to the patient's safety

The appropriate personnel from the site and Novartis will assess whether investigational treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

Patients who discontinue investigational treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated by an asterisk (*) in Table 6-1 or Table 6-2. If they fail to return for these assessments for unknown reasons, every effort (*e.g.* telephone, e-mail, letter) should be made to contact them as specified in Section 5.5.11.

The investigator must also contact the IRT to register the patient's discontinuation from investigational treatment.

5.5.10 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts and does not allow analysis of already obtained biologic material.

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information. Investigational treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

5.5.11 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

5.5.12 Emergency breaking of assigned treatment code

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, investigational treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/ she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Global Trial Lead (GTL) that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact his/ her backup in cases of emergency when he/ she is unavailable. The investigator will provide protocol number, investigational treatment name if available, patient number, and instructions for contacting the local Novartis Country Pharma Organization CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case an emergency treatment code break is required at a time when the investigator and backup are unavailable.

5.5.13 Study completion and post-study treatment

A patient who completes the baseline visit, is randomized to study drug, continues to participate in all required study visits post randomization up to Day 113 and completes all required assessments is considered a study completer. Site personnel will complete the randomized treatment epoch completion form recording the date the patient last took study medication and whether the patient completed or discontinued from the study.

Enrollment in the screening portion of the study will be closely monitored when the 50^{th} patient per cohort has been randomized. Patients still within the screening portion of the study will terminate their participation after the 60^{th}, and last, patient per cohort has been randomized.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care does not require any special treatment but it is recommended not to initiate any live vaccination or biologic treatment until 3 months after the last dose of study treatment.

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 (screening epoch [Epoch 1] and the randomized treatment epoch [Epoch 2]) and Table 6-2 (randomized withdrawal epoch [Epoch 3] and open-label treatment epoch [Epoch 4]) list all of the assessments and indicate with an "x" when the visits are performed.

Patients are to be seen for all visits, preferably on the designated day. The proposed visit day is displayed in Table 6-1 and Table 6-2.

Patients who prematurely withdraw from Epoch 2 for any reason should be scheduled for a visit when all the assessments listed for Day 113 will be performed.

Patients who prematurely withdraw from Epoch 3 for any reason should be scheduled for a visit when all the assessments listed for Day 281 will be performed.

Patients who prematurely withdraw from Epoch 4 for any reason should be scheduled for a visit when all the assessments listed for Day 785 will be performed.

If a patient refuses to return for these assessments or is unable to do so, every effort should be made to contact him/ her by telephone to determine the reason for discontinuation.

At a minimum, patients will be contacted for safety evaluations and a follow-up visit or phone call for SAEs must be performed 30 days following Investigational treatment discontinuation (TD), Premature subject withdrawal (PSW) or 8 weeks after last injection of study drug, whichever is later.

Documentation of attempts to contact the patient should be recorded in the patient record.

Table 6-1 Assessment schedule:
Screening epoch (Epoch 1) and randomized treatment epoch (Epoch 2)

Epoch	**Screening (Epoch 1)**	**Randomized treatment epoch (Epoch 2)**						
Visit	**1**	**101**	**102**	**103**	**104**	**105**	**199 and/ or PSW**	**Safety follow-up**
Week		**1**	**3**	**5**	**9**	**13**	**17**	
Day	**-84 to -3**	**1**	**15**	**29**	**57**	**85**	**113**	**PSW +30 or 8 weeks after last injection[1]**
Informed consent	X							
Informed consent for pharmacogenetic sampling[2]	X							
Participation in previous study CACZ885D2203/ MPP treatment plan CAC/885D2207M	X							
Demography	X							
Inclusion/Exclusion Criteria	X	X						
Relevant medical history/ current medical conditions	X							
Prior and concomitant medications (*including vaccination status*)	X	X	X	X	X	X	X	
Surgical and medical procedures	X	X	X	X	X	X	X	
Disease characteristics	X							
Determination of TB status: QuantiFERON®-TB Gold in Tube (QFT-GIT) assay, PPD skin test and/ or chest X-ray (as stipulated by local guidelines)	X							
Hepatitis B and C screen	X							
HIV screen	X							

Epoch	**Screening (Epoch 1)**	**Randomized treatment epoch (Epoch 2)**						
Visit	**1**	**101**	**102**	**103**	**104**	**105**	**199 and/ or PSW**	**Safety follow-up**
Week		**1**	**3**	**5**	**9**	**13**	**17**	
Day	**-84 to -3**	**1**	**15**	**29**	**57**	**85**	**113**	**PSW +30 or 8 weeks after last injection[1]**
Pregnancy test – Serum* (for females of child bearing potential)	X							
Pregnancy test – Urinalysis (for females of child bearing potential)		X						
Physical examination*	S	S		S	S	S	S	
Height	X				X[3]		X[3]	
Weight*	X	X	X	X	X	X	X	
Blood pressure and pulse*	X	X	X	X	X	X	X	
Body temperature*	X	X	X	X	X	X	X	
ECG*	X						X	
Index flare onset		X						
PGA	X	X	X	X	X	X	X	
Physician's severity assessment of key disease-specific signs and symptoms		X	X	X	X	X	X	
Review eDiary instructions	S							
PPGA[4]	X	X	X	X	X	X	X	
AIDAI[4]	X	X	X	X	X	X	X	
SF-12® (to be completed by patients ≥18 years of age at Baseline)		X		X			X	
CHQ-PF50© (to be completed by patients >5 <18 years of age at Baseline)		X		X			X	

Epoch	**Screening (Epoch 1)**	**Randomized treatment epoch (Epoch 2)**						
Visit	**1**	**101**	**102**	**103**	**104**	**105**	**199 and/ or PSW**	**Safety follow-up**
Week		**1**	**3**	**5**	**9**	**13**	**17**	
Day	**-84 to -3**	**1**	**15**	**29**	**57**	**85**	**113**	**PSW +30 or 8 weeks after last injection[1]**
SDS v3		X					X	
Hematology*	X	X	X	X	X	X	X	
Blood chemistry*	X	X	X	X	X	X	X	
Urinalysis*	X	X	X	X	X	X	X	
CRP (local lab)*	X	X	X	X	X	X	X	
SAA*	X	X	X	X	X	X	X	
PD sample (total IL-1β)* (*pre-dose*)		X	X	X	X	X	X	
PK sample (canakinumab)* (*pre-dose*)		X	X	X	X	X	X	
IG sample* (*pre-dose*)		X		X			X	
Pharmacogenetic sample[2]		X						
Contact IRT*	X	X	X	X	X	X	X	
Administration of double-blind randomized treatment		X		X	X	X		
Administration of blinded-escape treatment[5]			X	X	X	X		
Administration of open-label treatment[6]				X	X	X		
Adverse events*		X	X	X	X	X	X	
Local tolerability*		X	X	X	X	X	X	
Screening phase disposition form		X						
Study phase completion form							X	

Epoch	**Screening (Epoch 1)**	**Randomized treatment epoch (Epoch 2)**						
Visit	**1**	**101**	**102**	**103**	**104**	**105**	**199 and/ or PSW**	**Safety follow-up**
Week		**1**	**3**	**5**	**9**	**13**	**17**	
Day	**-84 to -3**	**1**	**15**	**29**	**57**	**85**	**113**	**PSW +30 or 8 weeks after last injection[1]**
Follow-up visit or phone call for SAEs*								X

TD = Investigational treatment discontinuation
PSW = Premature subject withdrawal
X = assessment to be recorded on clinical data base
S = assessment to be recorded on source documentation
*These assessments are also to be conducted for patients who discontinue
#These assessments are source documentation only and will not be entered into the CRF
[1] To be performed 30 days following Day 113 or PSW or 8 weeks after last injection of investigational drug, whichever is later for all patients ***not*** entering Epoch 3
[2] Only applicable for patients > 16 years of age
[3] Only applicable for pediatric patients
[4] The AIDAI and PPGA will be completed by the patient on an electronically diary daily from Screening till TD or PSW
[5] Applicable for patients whose index flare has not resolved by Day 15. Blinded-escape add-on treatment may be initiated from Day 8 to Day 28
[6] Applicable for patients on randomized treatment who flare on/ after Day 29 or patients on blinded-escape who will still have “mild”, “moderate” or “severe” disease activity (PGA ≥2 [clinical flare] and CRP ≥30 mg/L [serological flare]) or re-flare

Table 6-2 Assessment schedule:
Randomized withdrawal epoch (Epoch 3) and open-label treatment epoch (Epoch 4)

Epoch	**Randomized withdrawal epoch (Epoch 3)**							**Open-label treatment epoch (Epoch 4)**										
Visit	**201**	**202**	**203**	**204**	**205**	**206**	**299/ PSW**	**301**	**302**	**303**	**304**	**305**	**306**	**307**	**308**	**309**	**399/ TD/ PSW**	**Safety follow-up**
Week	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**41**	**49**	**57**	**65**	**73**	**81**	**89**	**97**	**105**	**113**	
Day	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**281**	**337**	**393**	**449**	**505**	**561**	**617**	**673**	**729**	**785**	**TD/ PSW +30 or 8 weeks after last injection[1]**
Prior and concomitant medications	X[2]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Surgical and medical procedures	X[2]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Inclusion/Exclusion Criteria	X[2]																	
Pregnancy test – Serum* (for females of child bearing potential)																	X	
Determination of TB status: QFT-GIT assay, PPD skin test and/ or chest X-ray (as stipulated by local guidelines)							X										X	
Physical examination*	S[2]	S		S	S	S	S		S	S	S	S	S	S	S	S	S	
Height	X[2]		X[3]		X[3]		X[3]		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	
Weight*	X[2]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Blood pressure and pulse*	X[2]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Body temperature*	X[2]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	

Epoch	**Randomized withdrawal epoch (Epoch 3)**							**Open-label treatment epoch (Epoch 4)**										
Visit	**201**	**202**	**203**	**204**	**205**	**206**	**299/ PSW**	**301**	**302**	**303**	**304**	**305**	**306**	**307**	**308**	**309**	**399/ TD/ PSW**	**Safety follow-up**
Week	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**41**	**49**	**57**	**65**	**73**	**81**	**89**	**97**	**105**	**113**	
Day	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**281**	**337**	**393**	**449**	**505**	**561**	**617**	**673**	**729**	**785**	**TD/ PSW +30 or 8 weeks after last injection[1]**
ECG*	X[2]						X										X	
PGA	X[2]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Physician's severity assessment of key disease-specific signs and symptoms	X[2]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
PPGA[4]	X[2]	X	X	X	X	X	X											
AIDAI[4]	X[2]	X	X	X	X	X	X											
SF-12® (*to be completed by patients ≥18 years of age at Baseline*)	X[2]			X			X											
CHQ-PF50© (*to be completed by patients >5 <18 years of age at Baseline*)	X[2]			X			X											
SDS v3	X[2]			X			X											
Hematology*	X[2]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Blood chemistry*	X[2]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Urinalysis*	X[2]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
CRP (local lab)*	X[2]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
SAA*	X[2]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	

Epoch	**Randomized withdrawal epoch (Epoch 3)**							**Open-label treatment epoch (Epoch 4)**										
Visit	**201**	**202**	**203**	**204**	**205**	**206**	**299/ PSW**	**301**	**302**	**303**	**304**	**305**	**306**	**307**	**308**	**309**	**399/ TD/ PSW**	**Safety follow-up**
Week	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**41**	**49**	**57**	**65**	**73**	**81**	**89**	**97**	**105**	**113**	
Day	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**281**	**337**	**393**	**449**	**505**	**561**	**617**	**673**	**729**	**785**	**TD/ PSW +30 or 8 weeks after last injection[1]**
PD sample (total IL-1β)* (*pre-dose*)	X[2]		X		X		X			X				X			X	
PK sample (canakinumab)* (*pre-dose*)	X[2]		X		X		X			X				X			X	
IG sample* (*pre-dose*)	X[2]						X			X				X			X	
Contact IRT*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Administration of re-randomized treatment	X		X		X													
Administration of open-label treatment[5]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		
Adverse events*	X[2]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Local tolerability*	X[2]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Screening phase disposition form	X[2]																	
Study phase completion form*							X										X	
Follow-up visit or phone call for SAEs*																		X

TD = Investigational treatment discontinuation
PSW = Premature subject withdrawal
X = assessment to be recorded on clinical data base
S = assessment to be recorded on source documentation
*These assessments are also to be conducted for patients who discontinue
#These assessments are source documentation only and will not be entered into the CRF
[1] To be performed 30 days following TD or PSW, or 8 weeks after last injection of investigational drug, whichever is later
[2] Only applicable for TRAPS patients rolling-over from CACZ885D2203/ CACZ885D2207M i.e. patients directly entering Epoch 3 following screening
[3] Only applicable for pediatric patients
[4] The AIDAI and PPGA will be completed by the patient on an electronically diary daily till Day 281 or PSW
[5] Patients up-titrated to q4w administration in Epoch 4, will come back every 4 weeks for unscheduled visits at Day 309, Day 365, Day 421, Day 477, Day 533, Day 589, Day 645, Day 701 and Day 757 in addition to the scheduled visits

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/ other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, ethnicity, source of patient referral, relevant medical history/ current medical condition present before signing informed consent. Where possible, diagnoses but not symptoms will be recorded.

Detailed information on the patient's vaccination status (to be recorded as part of prior medication), disease diagnosis and disease related prior medications/ surgical and medical procedures before signing informed consent will also be collected.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

All baseline characteristics to be collected are also listed in Table 6-1.

6.2.1 Determination of tuberculosis status

Determination of TB status will be required before administration of study treatment (Table 6-1) and needs to be re-assessed at Day 281 and Day 785 (Table 6-2).

Selection of the most suitable test or combination of tests for detection of *M. tuberculosis* infection as listed in Section 6.2.1.1, Section 6.2.1.2 and Section 6.2.1.3 should be made as defined by local guidelines.

Any significant findings at screening will be recorded in the "Relevant medical history/ Current medical conditions" section of the eCRF.

Any significant findings *after providing written informed consent* for participation in the study must be recorded as Adverse Events.

6.2.1.1 QuantiFERON®-TB Gold In-Tube assay

A QuantiFERON®-TB Gold In-Tube (QFT-GIT) assay may be carried out by the Central Laboratory to assess the TB status of patients.

This blood-based assay is specific for *Mycobacterium tuberculosis* and is not influenced by previous Bacillus Calmette-Guérin (BCG) vaccination or exposure to other Mycobacteria species. This test, in contrast to the Purified Protein Derivative (PPD) skin test, is also insensitive to a booster effect since the patient is not exposed to the vaccine. The assay measures the production of interferon-gamma and puts it into relation to a negative and a positive control sample. Further information is given by (Manuel and Kumar 2008).

Details about sample processing are to be described in the Central Laboratory Manual.

6.2.1.2 PPD skin test

A PPD skin test may be initiated to evaluate for an occult infection with TB if required by local regulations. The test dose is bioequivalent to 5 tuberculin units (or as according to local standard practice) of standard PPD usually injected intradermally into the volar surface of the forearm. The injection site will be cleansed and the PPD extract will then be injected into the most superficial layer under the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

A reaction will be measured in millimeters of induration (hard swelling) after 48h – 72h. A PPD skin induration >5 mm is interpreted as positive result. This will determine whether the patients have had a significant reaction to the PPD skin test.

In case of a positive PPD skin test result and the absence of clinical signs of active tuberculosis and no history of BCG vaccination, the clinical investigator will, according to local guidance, decide whether this subject should undergo further clinical, laboratory and radiological examinations before deciding to initiate prophylactic treatment for latent TB infection. Level of TB risk is defined in Appendix 4. A chest x-ray or QFT-GIT assay is however required to further investigate the nature of the positive PPD skin test as recommended by many local guidelines. In case of a negative confirmatory test, the patient is eligible for participation/ continuation in the study and no further clinical investigations are needed.

Patients with a positive PPD skin test result may be eligible for participation/ continuation only if they have a negative chest x-ray (Section 6.2.1.3) or negative QFT-GIT assay (refer to Section 6.2.1.1).

The investigator will either obtain PPD skin tests on his own and be reimbursed by Novartis for its cost or be supplied with them by the Novartis affiliate, depending on the local Novartis policy.

6.2.1.3 Chest x-ray

A chest x-ray may be performed if required for a complete TB workup per local regulations.

6.2.2 Hepatitis screen, HIV screen

In order to exclude an active infection such as hepatitis or HIV infection, all patients will undergo appropriate testing at the Screening visit unless a negative serology is available within 3 months prior to screening.

All subjects will be screened for Hepatitis B surface antigen (HBsAg) and Hepatitis C virus (HCV) antibodies unless negative serologies are available within 3 months prior to screening. A copy of the lab report must be placed in the patient's file.

Evaluation for HIV seropositivity will be performed, and if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot. Appropriate subject counseling will be made available by the investigator in the event of a positive finding. Notification of

state and federal authorities, as required by law, will be the responsibility of the investigator. A copy of the lab report must be placed in the patient's file.

6.3 Treatment exposure and compliance

Compliance is expected to be 100% since study treatment will be administered subcutaneously by the investigator or study personnel.

6.4 Efficacy

Patients for whom study treatment must be permanently discontinued as detailed in Section 5.5.9 do not need to complete any of the efficacy assessments listed in this Section 6.4.

6.4.1 Physician's global assessment of Disease activity (PGA)

Physician's global assessment of disease activity (PGA) will be assessed as shown in Table 6-1 and Table 6-2.

PGA will be performed prior to the CRP results will be available from the local lab in order to prevent bias in the evaluation.

It is encouraged that one investigator assess the same patient throughout the study to ensure consistency between assessments.

The physician's global assessment will be based on a 5-point scale:

- 0 = None (no) disease associated clinical signs and symptoms
- 1 = Minimal disease associated signs and symptoms
- 2 = Mild disease associated signs and symptoms
- 3 = Moderate disease associated signs and symptoms
- 4 = Severe disease associated signs and symptoms

6.4.2 Physician's severity assessment of key disease-specific signs and symptoms

Physician's severity assessment of key disease-specific signs and symptoms will be assessed as shown in Table 6-1 and Table 6-2.

It is encouraged that one investigator assess the same patient throughout the study to ensure consistency between assessments.

Key signs and symptoms will differ for each individual condition. The following signs and symptoms will be assessed:

1. TRAPS: skin rash, musculoskeletal pain, abdominal pain, eye manifestations
2. HIDS: lymphadenopathy, aphtous ulcers, abdominal pain
3. crFMF: chest pain, abdominal pain, arthralgia/arthritis, skin rash

Physician's severity assessment of key disease-specific signs and symptoms will be based on a 5-point scale:

- 0 = Absent

- 1 = Minimal
- 2 = Mild
- 3 = Moderate
- 4 = Severe

Fever (body temperature ≥38°C [100.4°F]), a key sign of disease activity will be assessed via the vital signs (see Section 6.5.2).

6.4.3 Inflammatory markers

C-reactive protein (CRP) and serum amyloid A (SAA) protein will be measured as shown in Table 6-1 and Table 6-2 for all patients regardless of age.

CRP will be measured at the local laboratory, including any unscheduled visits. CRP value will be standardized to a normal range of 0-10 mg/L. A back-up blood sample should be withdrawn and shipped to the central lab for storage for central CRP re-testing if deemed necessary.

SAA will be measured at the central laboratory.

6.4.4 Resolution of the index flare

Resolution of the index flare is defined as follows:

- PGA <2, and CRP within normal range (≤10 mg/L) or reduction by at least 70% from baseline

The resolution of the index flare will be assessed at Day 15.

6.4.5 New disease flare

From Day 29 onwards, a new disease flare is defined as **simultaneous** occurrence of a clinical flare and a serological flare defined as follows:

- PGA ≥2 (clinical flare)
- CRP ≥30 mg/L (serological flare)

For patients who achieved resolution of index flare at Day 15, this definition will be applied from Day 16.

6.4.6 Auto-inflammatory Disease Activity Index (AIDAI)

The Auto-inflammatory Disease Activity Index (AIDAI) score is a valid and simple tool for assessing disease activity in TRAPS/ HIDS/ crFMF and CAPS. This tool is easy to use in clinical practice and has the potential to be used as a standard efficacy measure in clinical trials (Piram et al. 2013).

The AIDAI will be collected on an electronic diary.

This instrument needs to be filled out by the patient (for children a parent can assist when necessary) daily from Screening till TD/ PSW. Patients will be instructed to complete the

AIDAI in the evening. The same evaluator (same patient or parent) should perform the assessment throughout the study for consistency.

The AIDAI diary contains 13 items as follows: (a) fever, ≥38°C (100.4°F); (b) overall symptoms; (c) abdominal pain; (d) nausea/vomiting; (e) diarrhea; (f) headaches; (g) chest pain; (h) painful nodes; (i) arthralgia or myalgia; (j) swelling of the joints; (k) eye manifestations; (l) skin rash; (m) pain relief drugs taken.

All items have to be scored as either yes or no.

6.4.7 Patient/ Parent's global assessment of disease activity (PPGA)

Patient's assessment of disease activity (PPGA) will be collected on an electronic diary.

This instrument needs to be filled out by the patient (for children a parent can assist when necessary) daily from Screening till TD/ PSW. Patients will be instructed to complete the PPGA in the evening after having completed the AIDAI (Section 6.4.6). The same evaluator (same patient or parent) should perform the assessment throughout the study for consistency.

The investigator or site staff will not be allowed to review the patient's electronic diary to ensure for unbiased data collection.

The PPGA is based on a 5-point scale:

- 0 = None/absent (no) disease associated clinical signs and symptoms
- 1 = Minimal disease associated signs and symptoms
- 2 = Mild disease associated signs and symptoms
- 3 = Moderate disease associated signs and symptoms
- 4 = Severe disease associated signs and symptoms

6.4.8 Health-related Quality of Life

Health-related quality of life (HRQoL) will be assessed by the following instruments:

- SF-12 Health Survey – Acute version 2 (SF-12v2) *to be completed by patients ≥18 years of age at Baseline*
- Child Health Questionnaire – Parent Form 50 (CHQ-PF50) *to be completed by patients >5 <18 years of age at Baseline*
- Sheehan Disability Scale version 3 (SDS v3)

The questionnaires should be completed by the patient and/or parents at the scheduled visits before any other clinical assessments. The patient and/or parent should be given sufficient space and time to complete the questionnaires. The study coordinator should check the questionnaires for completeness and encourage the patient and/or parent to complete any missing responses. The questionnaires will be completed on an electronic device, e.g. tablet.

6.4.8.1 Medical Outcome Short Form (12) Health Survey – Acute version 2 (SF-12v2)

The purpose of SF-12v2 in this study is to assess the physical and mental functioning of adult patients (patients ≥18 years of age at baseline) in this study.

The SF-12v2 is a widely used instrument to measure generic health status. This 12-item questionnaire yields an 8-scale health profile as well as summary measures of individual patients. It has proven to be useful in monitoring general and disease-specific populations, comparing the relative burden of different diseases, differentiating the health benefits produced by different treatments, and in screening of individual patients.

The SF-12® measures the impact of disease on overall quality of life and consists of eight subscales (physical function, pain, general and mental health, vitality, social function, physical and emotional health) which can be aggregated to derive a physical-component summary score and a mental-component summary score. Scores are determined with the use of norm-based methods which standardize scores based on an assessment of the general U.S. population free of chronic conditions.

The SF-12v2 will be completed at visits shown in Table 6-1 and Table 6-2.

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

The CHQ-PF50 is an instrument used to measure HRQoL in children 5 to 17 years of age from a parent's perspective. This questionnaire is to be completed by the parent with no input from the patient.

The CHQ-PF50 has been shown to provide reliable and valid summary (physical and psychosocial health) scores for a 14-concept health status and for well-being concepts. This instrument is comprised of scales specifically developed for children and adolescents. The questionnaire measures the following concepts: Physical functioning, Role/social emotional, Role/social behavior, Role/social physical, Bodily pain, General behavior, Mental health, Self-esteem, General health perception, Change in health, Parental impact – emotional, Parental impact – time, Family activities, and Family cohesion.

If during participation in this study, the patient turns 18, the parent would continue to complete the CHQ-PF50 until the time the patient completes this study.

The CHQ-PF50 will be completed by the parent at visits shown in Table 6-1 and Table 6-2.

6.4.8.3 Sheehan Disability Scale (SDS)

The Sheehan Disability Scale (SDS) was developed to assess functional impairment in three inter-related domains; work/ school, social and family life. It is used by researchers and practicing clinicians.

The SDS is a brief self-reporting tool: The patient rates the extent to which work/ school, social life or family responsibilities are impaired by his or her symptoms on a 10-point visual analog scale. This 10-point visual analog scale uses spatiovisual, numeric and verbal

descriptive anchors simultaneously to assess disability. The range of anchor options addresses the various ways that individuals approach rating a continuum.

The SDS will be completed at visits shown in Table 6-1 and Table 6-2.

6.4.9 Appropriateness of efficacy assessments

The efficacy assessments selected are considered standard for this indication/ patient population and have previously been used in the respective canakinumab PoC studies or have been validated for use in hereditary recurrent fever syndromes (Piram et al. 2013).

6.5 Safety

The safety assessments presented in this Section 6.5 are mandatory for all patients including those for whom study treatment must be permanently discontinued as detailed in Section 5.5.9.

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A complete physical examination will be performed at Screening (Visit 1).

A short physical exam will include the examination of general appearance and vital signs. A short physical exam will be at all visits starting from Randomization (Visit 101) except where a complete physical examination is required (see above).

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.

6.5.2 Vital signs

Vital signs will be obtained as shown Table 6-1 and Table 6-2. They will include blood pressure (BP), pulse and body temperature measurements.

Systolic and diastolic BP and radial pulse rate will be assessed after the patient has rested in the supine position for at least 3 minutes. Blood pressure should be assessed on the same arm each time measurements are taken. These data will be recorded in the CRF.

Measurement of blood pressure in the pediatric population should be done with the appropriate cuff size (see Appendix 1 for more details) and toward the end of the scheduled visit, thereby avoiding an increase in blood pressure which could be due to a white coat effect. Moreover, the investigator should check whether the pediatric patient is calm before taking the blood pressure reading.

Body temperature should be measured by validated thermometers as commonly used by sites in the respective patient population. The same type of thermometer should be used throughout the study.

6.5.3 Height and weight

Height in centimeters (cm) and body weight [to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes] will be measured as shown in Table 6-1 and Table 6-2.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected with the exception of CRP which will be assessed locally. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.1 Hematology

The hematology panel will include: Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential including lymphocytes, monocytes, neutrophils, eosinophils, basophils, and platelet count will be measured. Absolute Neutrophil Count (ANC) will be calculated by the laboratory.

Blood volume drawn for pediatric patients will be reduced according to age and weight and is specified in the central laboratory manual.

Hematology samples are to be collected at visits shown in Table 6-1 and Table 6-2.

6.5.4.2 Clinical chemistry

The chemistry panel will include: Albumin, alkaline phosphatase, total and differentiated bilirubin, calcium, chloride, fasting total cholesterol (including LDL and HDL), creatinine, creatinine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), α-amylase, γ-glutamyltransferase (GGT), fasting glucose, sodium, potassium, inorganic phosphorus, total protein, lactate dehydrogenase (LDH), triglycerides, magnesium, blood urea nitrogen (BUN), and uric acid.

Blood volume drawn for pediatric patients will be reduced according to age and weight and is specified in the central laboratory manual.

Clinical chemistry samples are to be collected at visits shown Table 6-1 and Table 6-2. The patient must be in a fasting state at the time of blood sampling.

6.5.4.3 Urinalysis

A midstream urine sample (approx. 30 ml) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

Semi-quantitative 'dipstick' evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood at visits shown in Table 6-1 and Table 6-2. Results of the 'dipstick' will be entered into the Urinalysis CRF.

If the dipstick result is positive for albumin, nitrite, leucocytes and/ or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts.

6.5.5 Electrocardiogram (ECG)

ECGs will be obtained as shown Table 6-1 and Table 6-2.

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12-lead ECGs are collected. The original ECGs on non-heat-sensitive paper and a certified copy on non-heat sensitive paper), appropriately signed, should be collected and archived at the study site.

Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings at baseline must be discussed with the sponsor before administration with investigational treatment.

Clinically significant abnormalities should be recorded on the relevant section of the medical history/ Current medical conditions/ AE eCRF page as appropriate.

6.5.6 Pregnancy and assessments of fertility

6.5.6.1 Female adult patients (≥18 years)

Female patients ≥18 years of age and of childbearing potential except those who are determined to be post-menopausal and not of child-bearing potential, are required to have a pregnancy test performed.

A serum pregnancy test must be performed at the central lab on samples collected from these patients as shown in Table 6-1 and Table 6-2. Urine pregnancy testing may be conducted locally at the site at randomization.

If a pregnancy test is positive, the patient must be discontinued from the study treatment and followed up according to Section 5.5.9.

6.5.6.2 Female adolescents (≥12 to <18 years)

All menarchal girls and their parents/ caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study. It is important to be sensitive in introducing this issue, as understanding and comprehension of puberty, sexual

activity, pregnancy and contraception is influenced by age, as well as factors such as precocity, socio-economic, educational and familial background. These discussions with the patient and her parents/ caregivers are therefore best performed by investigators familiar with the adolescent and her family and should be guided by requirements of the local regulatory authorities. These discussions should take into account the socio-economic, cultural factors and religious beliefs of the adolescent participant and her family. The investigator should also discuss the management of the pregnancy test results with the patient and her parents/ caregivers. The privacy of the adolescent should be considered in accordance with the local law and ethics.

Female patients of child-bearing potential, who are or might become sexually active, must be informed of the need to prevent pregnancy during the study. Women should use effective contraception in accordance with locally approved prescribing information. For details about acceptable effective contraception, refer to exclusion criterion #14 in Section 4.2. The decision on the contraceptive method should be reviewed at least every 3 months to evaluate the individual need and compatibility of the method chosen.

6.5.6.3 Female pediatric patients (<12 years)

No pregnancy tests are required.

6.5.7 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

6.6 Other assessments

6.6.1 Resource utilization

No resource/ healthcare utilization information will be collected on patients entered into this study.

6.6.2 Pharmacokinetics

Canakinumab concentrations will be analyzed in serum by means of a competitive ELISA assay [redacted]

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

For each scheduled PK sample, 2 mL of blood will be drawn into a plain barrier tube to obtain 1 mL serum (the indicated blood volume will apply for patients > 16 years of age. For younger patients, a minimum of 1 mL of blood can be drawn in order to obtain 0.5 mL of serum). The sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. The sample will be split into two aliquots to be transferred into polypropylene screw-cap tubes. Serum tubes will be frozen within 90 min of venipuncture and kept at ≤ -18°C pending shipment on dry ice. One of the two serum samples is to be kept at the study site as a backup while the other one will be shipped to the analytical center.

Actual time of dosing and actual times of blood collection have to be recorded on the PK blood collection eCRF page. PK samples will be collected as shown in Table 6-1 and Table 6-2. For a detailed description of blood sampling, handling, labeling and shipment instructions please refer to the Laboratory Manual and the Blood Sampling Log Appendix 3.

If anaphylactic reactions occur after injection, two more samples (at the time of the event and 8 weeks later) need to be taken.

6.6.3 Pharmacodynamics

Total IL-1β (sum of free and bound to canakinumab) will be analyzed in serum by means of a competitive ELISA assay, [redacted]

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

For each scheduled PD sample, 3 mL of blood will be drawn into a plain barrier tube, to obtain 1.5 mL serum (the indicated blood volume will apply for patients > 16 years of age. For younger patients, a minimum of 1.5 mL blood can be drawn in order to obtain 0.7 mL of serum). The sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. The sample will be split into two aliquots to be transferred into freezer-proof polypropylene screw-cap tubes. Serum tubes will be frozen within 90 min of venipuncture and kept at ≤ -18°C pending shipment on dry ice. One of the two serum samples is to be kept at the study site as a backup while the other one will be shipped to the central lab.

Actual time of dosing and actual times of blood collection have to be recorded on the PD blood collection eCRF page. PD samples will be collected as shown in Table 6-1 and Table 6-2.

For a detailed description of blood sampling, handling, labeling and shipment instructions please refer to the Laboratory Manual and the Blood Sampling Log Appendix 3.

If anaphylactic reactions occur after injection, two more samples (at the time of the event and 8 weeks later) need to be taken.

6.6.4 Pharmacogenetics/pharmacogenomics

6.6.4.1 Pharmacogenetics

The study includes an optional pharmacogenetic component which requires a separate signature if the patient agrees to participate. It is required as part of this protocol that the Investigator presents these options to the patient.

[redacted]

[redacted]

One 10 ml blood sample will be collected at study Baseline in an EDTA tube. After collection, the sample must be inverted several times to prevent clotting. If the blood draw at Baseline is missed, the sample should be taken at the next visit that a blood draw is already scheduled. Only one blood sample should be taken from patients > 16 years of age for this pharmacogenetic study. These samples will be shipped to the central lab for DNA extraction. The extracted DNA will then be transferred to [redacted]

Lab manuals will be provided with detailed information on sample collection, handling, and shipment. The sample collection date and exact time must be entered on the sample collection CRF page.

[redacted]

6.6.4.2 Pharmacogenomics

Not applicable.

6.6.5 Immunogenicity

Anti-ACZ885 antibody concentrations will be assessed in serum.

For each scheduled IG sample, 2 mL of blood will be drawn into a plain barrier tube, to obtain 1 mL serum (the indicated blood volume will apply for patients > 16 years of age. For younger patients, a minimum of 1 mL of blood can be drawn in order to obtain 0.5 mL of serum). The blood sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. The sample will be split into two aliquots to be transferred into freezer-proof polypropylene screw-cap tubes. Serum tubes will be frozen within 90 minutes of venipuncture and kept at ≤ -18°C pending shipment on dry ice.

Actual time of dosing and actual times of blood collection have to be recorded on the IG blood collection eCRF page. IG samples will be collected as shown in Table 6-1 and Table 6-2.

For a detailed description of blood sampling, please refer to the Laboratory Manual and the Blood Sampling Log Appendix 3.

If anaphylactic reactions occur after injection, two more samples (at the time of the event and 8 weeks later) need to be taken.

6.6.6 Other biomarkers

No other biomarkers will be collected on patients entered into this study.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included in Appendix 1.

AEs should be recorded in the AEs CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information.

- the severity grade:
  a. mild: usually transient in nature and generally not interfering with normal activities
  b. moderate: sufficiently discomforting to interfere with normal activities
  c. severe: prevents normal activities
- its relationship to the
  a. investigational treatment (no/yes), or
  b. other study treatment (non-investigational) (no/yes), or
  c. both and/ or indistinguishable

- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/ not resolved should be reported.
- whether it constitutes a serious AE (SAE – See Section 7.2 for definition of SAE)
- action taken regarding investigational treatment.
  All AEs should be treated appropriately. Treatment may include one or more of the following:
  a. no action taken (i.e. further observation only)
  b. investigational treatment dosage adjusted/ temporarily interrupted
  c. investigational treatment permanently discontinued due to this adverse event
  d. concomitant medication given
  e. non-drug therapy given
  f. patient hospitalized/patient's hospitalization prolonged
- its outcome (not recovered/ not resolved; recovered/ resolved; recovering/ resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any AE (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  a. routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)

b. elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent form
c. treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
d. social reasons and respite care in the absence of any deterioration in the patient's general condition

- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see Annex IV, ICH-E2D Guideline).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

If all AEs (serious and non-serious) are captured on the CRF, SAEs are monitored continuously and have also special reporting requirements; see Section 7.2.2.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days following TD or PSW, or 8 weeks after last injection of study drug, whichever is later must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded in English on the paper Serious Adverse Event Report Form or the electronic Serious Adverse Event Form within the Oracle Clinical/Remote Data Capture (OC/RDC) system (where

available). The Investigator must assess the relationship to each specific component of the study treatment (if the study treatment consists of several components).

SAEs (initial and follow-up) that are recorded *on the paper SAE form* should be faxed within 24 hours of awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE

SAEs (initial and follow-up) that are recorded *electronically* in the OC/RDC system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after investigator signature or 24 hours after entry, whichever occurs first.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities/ adverse events have to be considered during the course of the study:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 14-1 (Appendix 2) for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 14-1 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 14-2.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation.

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory should then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded on appropriate CRF pages, including the liver event overview CRF pages.

7.4 Renal safety monitoring

To ensure patient safety and enhance reliability in determining the nephrotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of renal events has to be followed.

The following categories of renal AEs have to be considered during the course of the study:

1. Serum event: confirmed (after ≥ 24h) increase in serum creatinine of ≥ 25% compared to baseline during normal hydration status
2. Urine event: New onset (≥1+) proteinuria, hematuria or glucosuria; or doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable).

Every renal laboratory trigger or renal event as defined in Table 7-1 should be followed up by the investigator or designated personnel at the trial site as summarized below.

Table 7-1 Specific Renal Alert Criteria and Actions

Renal event	Actions
Serum event	
Serum creatinine increase 25-49% compared to baseline	• Confirm 25% increase after 24-48h • Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥50 % compared to baseline	• Follow up within 24-48h if possible • Consider drug interruption • Consider patient hospitalization /specialized treatment
Urine event	
New dipstick proteinuria ≥1 + Albumin- or Protein-creatinine ratio increase ≥2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥ 3 mg/mmol; Protein-creatinine ratio (PCR) ≥150 mg/g or >15 mg/mmol	• Confirm value after 24-48h • Perform urine microscopy • Consider drug interruption / discontinuation
New dipstick glucosuria ≥1 + not due to diabetes	• Blood glucose (fasting) • Perform serum creatinine, ACR
New dipstick hematuria ≥1 + not due to trauma	• Urine sediment microscopy • Perform serum creatinine, ACR

For all renal events:

1. Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed
2. Monitor patient regularly (frequency at investigator's discretion) until either:
   - Event resolution: sCr within 10% of baseline or PCR within 50% of baseline, or
   - Event stabilization: sCr level with ±10% variability over last 6 months or PCR stabilization at a new level with ±50% variability over last 6 months.

7.5 Pregnancy reporting

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyse data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to US CFR 21Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff (or CRO working on behalf of Novartis) review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Diary data will be entered into an electronic diary by the patient. The system will be supplied by a vendor who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all investigational treatment dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

8.5.1 Infection Adjudication Committee

An external, independent Infection Adjudication Committee (IAC) has been formed on a program level and will review pertinent data from this trial.

The mission of the canakinumab IAC is to independently and blindly review, evaluate and categorize new reports of pre-defined infections as they become available during the conduct of this trial.

The members, detailed mission and procedures of the IAC are detailed in the IAC charter which is available upon request.

8.5.2 Malignancy Adjudication Committee

An external, independent Malignancy Adjudication Committee (MAC) has been formed on a program level and will review pertinent data from this trial.

The mission of the MAC is to independently and blindly review, evaluate and categorize reports of malignancy events across all potential indications and therapeutic areas in the canakinumab development program.

The members, detailed mission and procedures of the MAC are detailed in the MAC Charter which is available upon request.

9 Data analysis

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

Randomized treatment epoch (Epoch 2):

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

For some efficacy endpoints and specific safety endpoints (like AEs or laboratory abnormalities), treatment arms will include

- canakinumab 150 mg q4w
- placebo
- canakinumab 150 mg– canakinumab 300 mg q4w
- placebo – canakinumab 150 mg q4w

In addition, patients in the canakinumab arm (150 mg q4w) flaring after Week 4 or placebo patients flaring after Week 4 or placebo patients flaring after receiving the first escape treatment will enter open-label escape and receive up to a maximum of 300 mg (or 4 mg/ kg) q4w until the end of study. Only descriptive safety data will be presented after patients enter open-label escape.

Randomized withdrawal epoch (Epoch 3):

Treatment arms for the safety and efficacy analyses will include, for canakinumab responders at the end of the epoch 2:

- canakinumab 150 mg q8w
- placebo.

And the two open-label treatment arms:

- canakinumab 150 mg q8w
- canakinumab 300 mg q8w

Open-label treatment epoch (Epoch 4):

Treatment arms for the safety and efficacy analyses will include (taken into account their regimen in Epoch 3):

- placebo - canakinumab 150 mg q8w
- placebo- canakinumab 150 mg q4w
- canakinumab 150 mg q8w - canakinumab 150 mg q8w
- canakinumab 150 mg q8w - canakinumab 150 mg q4w
- canakinumab 150 mg q8w
- canakinumab 300 mg q8w
- canakinumab 300 mg q8w – canakinumab 300 mg q4w

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. 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.

9.1 Analysis sets

The **Randomized Set** Epoch 2, respectively Epoch 3 will consist of all patients who are randomized in the randomized treatment epoch (Epoch 2), respectively 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, respectively Epoch 3 will consist of all randomized patients in the randomized treatment epoch, respectively in the randomized withdrawal epoch who received at least one dose of study drug. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization in each epoch.

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 **Safety Set** Epoch 2, Epoch 3, Epoch 4 will consist of all patients that received study treatment in Epoch 2, resp. Epoch 3, resp. Epoch 4 and had at least one post-baseline safety assessment. Patients will be analyzed according to treatment received. Of note, the statement that a subject had no AEs also constitutes a safety assessment.

9.2 Patient demographics and other baseline characteristics

Summary statistics will be provided for demographic and baseline characteristics by study cohort and treatment group in the randomized treatment epoch (Epoch 2), the randomized withdrawal epoch (Epoch 3) and open-label treatment epoch (Epoch 4).

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.

9.3 Treatments

The exposure to investigational treatment (number of doses) and duration of exposure (days) during this study will be summarized by cohort, epoch, treatment group and listed for the Safety Set.

The number and percentage of patients taking concomitant medication, rescue medication will be summarized by cohort, epoch, treatment group and ATC class.

9.4 Analysis of the primary variable(s)

All efficacy evaluations will be performed on the FAS.

9.4.1 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 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 ≥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 crossed-over from Placebo arms to canakinumab, or discontinued from the study due to any reason prior to evaluating the primary endpoint will be considered as non-responders.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary hypothesis tested will be the superiority of canakinumab dose (150 mg 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 with responder rate at Week 16 in canakinumab dose 150 mg s.c. (or 2 mg/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 150mg 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 97.5% confidence interval will be presented.

9.4.3 Handling of missing values/censoring/discontinuations

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 to evaluating the primary endpoint will be considered as non-responders.

9.4.4 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

9.4.5 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; i.e.,

- 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 where the primary analysis in the randomized treatment epoch will be repeated on the per-protocol set; i.e., excluding patients 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.

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 responder except if new flare occurs from Day 15 onward in Epoch 2.

9.5 Analysis of secondary variables

9.5.1 Secondary efficacy variables

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 including 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).

Testing strategy

If the primary objective is achieved, all secondary endpoints in the randomized treatment epoch (Epoch 2) will be assessed in a hierarchical testing procedure to evaluate the superiority of canakinumab s.c. q4w over placebo. This is performed in order to control the overall Type I error rate ($\alpha = 0.025$, one sided tests) in the evaluation of these secondary efficacy variables. Testing was continued as long as each test showed statistical significance at the 2.5% level.

The following hypotheses will be included the closed testing procedure:

Primary objective: H_1 (see Section 9.4.2).

Secondary objectives:

- H_2: Canakinumab 150 mg q4w is not different to placebo with respect to the percentage of patients with PGA < 2 at Week 16.
- H_3: Canakinumab 150 mg q4w is not different to placebo with respect the percentage of patients with CRP ≤10 mg/L at Week 16.
- H_4: Canakinumab 150 mg q4w is not different to placebo with respect the percentage of patients with SAA ≤10 mg/L at Week 16.

If all secondary objectives are achieved in the randomized treatment epoch, then the secondary objective in the randomized withdrawal epoch will be tested.

H_5: Canakinumab 150 mg q8w is not different to placebo with respect to the percentage of responders (absence of new flares) at Week 40.

Physician's global assessment of disease activity

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 effect for each cohort. 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 to evaluating the endpoint at week 16 will be considered as having PGA ≥2. In case of convergence issues then Firth's method will be used in the logistic regression model. If 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 ≤10 mg/L at Week 16 will be analyzed using a logistic regression model with treatment group, and baseline CRP values (log(e) transformation) as effect for each cohort. 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 to evaluating the endpoint at week 16 will be considered as having CRP >10 mg/L. In case of convergence issues then Firth's method will be used in the logistic regression model.

If convergence issue is still not resolved then Canakinumab treatment group will be compared to placebo with respect to the proportion of patients with CRP ≤10 mg/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 ≤10 mg/L at Week 16 will be analyzed using a logistic regression model with treatment group and baseline SAA values as effect for each cohort. 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 to evaluating the endpoint at week 16 will be considered as having SAA >10 mg/L. In case of convergence issues then Firth's method will be used in the logistic regression model. If convergence issue is still not resolved then Canakinumab treatment group will be compared to placebo with respect to the proportion of patients with SAA ≤10 mg/L at Week 16 will be analyzed using the Fisher's exact test.

Maintenance of clinically meaningful response

Responder in the randomized withdrawal epoch is defined as no flare between week 16 and week 40. The canakinumab 150 mg 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.

9.5.2 Exploratory efficacy variables

Exploratory efficacy variables will be analyzed separately for each independent cohort (TRAPS, HIDS, crFMF). Continuous variables will be summarized by mean, standard deviation, median, minimum, maximum, 25% and 75% quartiles, and number of patients with non-missing data. Categorical variables will be summarized by absolute frequencies and percentages.

Inflammatory parameters (CRP, SAA)

CRP and SAA will be summarized descriptively by visit for each cohort, epoch and by treatment arm.

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

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 response to treatment, investigator's global assessment of disease control, patient/parent global assessment of disease control, patient/parent global assessment of disease activity,

patient/parent assessment of flare severity, patient/parent severity assessment of the key disease-specific signs and symptoms will be presented in frequency tables by visit for each cohort and treatment group.

Between-treatment differences for the proportion of patients with no PGA disease activity, no PPGA disease activity at Week 16 will be analyzed using a Fisher's exact test for each cohort.

Episodes of Fever

Number and duration of fever episodes collected in patient's diaries will be summarized within each cohort and treatment group. Plots of fever episodes per patient over time and treatment group will also be presented.

Rescue medication (Corticosteroids and NSAIDs)

Corticosteroids and NSAIDs levels will be summarized descriptively by visit for each cohort and by treatment group.

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 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.

Blinded escape

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

Auto-Inflammatory Disease Activity Index (AIDAI)

Symptoms evaluated in the AIDAI diary will be summarized with each cohort and epoch.

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

The two treatment groups (150 mg 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.

SF-12 Health Survey (SF-12)

SF-12 scores will be summarized by epoch, visit and treatment arms within each cohort. Only patients ≥18 years of age at baseline will be part of the analyses.

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

Descriptive statistics will be used to summarize patient responses on the CHQ-PF50© Questionnaire by epoch, treatment, total score 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 domains and global functional impairment score will be summarized by epoch, visit and treatment arms within each cohort.

Number of flares

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

9.5.3 Safety variables

All safety evaluations will be performed on the Safety set.

9.5.3.1 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 and treatment group, 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. Exposure adjusted incidence rate of AEs will also be provided. 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 SMQ. Adverse event analyses will be adjusted for treatment group exposure in each epoch.

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.

9.5.3.2 Laboratory data

Laboratory parameters will be summarized by presenting descriptive statistics for the absolute values, change from baseline for each cohort, epoch and treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values in each 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.

In addition, laboratory values collected during the open-label escape period in the randomized treatment epoch will separately be listed.

9.5.3.3 Vital signs

Vital signs will be summarized by presenting descriptive statistics for the absolute values and changes from baseline for each cohort, epoch and treatment group. All information collected will be listed by patient and abnormal values will be flagged.

9.5.3.4 ECG

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

9.5.3.5 Immunogenicity

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

9.5.4 Resource utilization

No resource/ healthcare utilization information will be collected on patients entered into this study.

9.5.5 Pharmacokinetics

Summary statistics (e.g. mean, standard deviation) and individual subject listing of serum concentration measurements of canakinumab at the assigned time points will be provided as surrogates of systemic exposure.

9.5.6 Pharmacogenetics/pharmacogenomics

9.5.6.1 Pharmacogenetics

The exploratory pharmacogenetic studies are designed to investigate the association between [redacted]

9.5.6.2 Pharmacogenomics

Not applicable

9.5.7 Biomarkers

Samples for biomarker analyses are not to be taken as part of this study.

9.5.8 PK/PD

A mixed effects modeling approach may be used to characterize the PK of canakinumab and its binding to IL-1β. The relationship between the population parameters such as CL/F and covariates (demographics, disease) may be investigated using graphical methods and simple regression models. Quality of individual fits to the dataset will be assessed, and individual model parameters (post-hoc estimates) may be obtained for each patient. Alternatively, in case the population based modeling may not be feasible, the analysis will be limited to the methodology based on predictive check, where the measures of systemic drug exposure (pre-dose trough levels) will be plotted against the data collected in previous trials.

9.6 Interim analyses

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.

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) (see also Section 10.4).

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 (see also Section 10.4).

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 (see also Section 10.4).

9.7 Sample size calculation

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.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/ IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/ IEC approval.

The study includes an optional pharmacogenetic component which requires a separate signature if the patient agrees to participate. It is required as part of this protocol that the Investigator presents this option to the patient. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these pharmacogenetic assessments will in no way affect the patient's ability to participate in the main research study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov.

For this study, the following CSRs will be prepared:

1. The first CSR will report all efficacy and safety data collected during the randomized double-blind treatment epoch (Epoch 2) up to 16 weeks
2. An Interim Analysis CSR may be prepared to support health authority interactions, as necessary. This CSR will report all efficacy and safety data collected during the randomized withdrawal/ dose-reduction epoch (Epoch 3)
3. The final CSR will report cumulative long term safety and efficacy data collected during all 4 epochs

Upon study completion and finalization of the final CSR the results of this trial will be either submitted for publication and/ or posted in a publicly accessible database of clinical trial results.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 should be followed.

12 References

References are available upon request

Aksentijevich I, Kastner DL (2011). Genetics of monogenic autoinflammatory diseases: past successes, future challenges. Nat. Rev. Rheumatol. 7, 469–478; published online 5 July 2011; doi:10.1038/nrrheum.2011.94.

De Benedetti F, Brunner HI, Ruperto N, et al (2012). Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012 Dec 20;367(25):2385-95.

Dinarello CA, Simon A, van der Meer JW (2012). Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. Nat Rev Drug Discov. 2012 Aug;11(8):633-52.

Drenth JP, van der Meer JW (2001). Hereditary periodic fever. N Engl J Med. 2001 Dec 13;345(24):1748-57.

Gattorno M, Obici L, Meini A et al (2012).Efficacy and Safety of Canakinumab in Patients with TNF Receptor Associated Periodic Syndrome. Arthritis Rheum. 2012 64(10) S322-S322 abstract 749.

Goldbach-Mansky R (2012). Immunology in clinic review series; focus on autoinflammatory diseases: update on monogenic autoinflammatory diseases: the role of interleukin (IL)-1 and an emerging role for cytokines beyond IL-1. Clin Exp Immunol. 2012 Mar;167(3):391-404.

Gul A, Ozdogan H, Erer B, et al (2012). Efficacy and Safety of Canakinumab in Adults with Colchicine Resistant Familial Mediterranean Fever. Arthritis Rheum. 2012 64(10) S322-S322 abstract 750.

Hoffman HM, Simon A (2009). Recurrent febrile syndromes: what a rheumatologist needs to know. Nat Rev Rheumatol. 2009 May;5(5):249-56.

Koné-Paut I, Lachmann HJ, Kuemmerle-Deschner JB, et al (2011). Sustained remission of symptoms and improved health-related quality of life in patients with cryopyrin-associated periodic syndrome treated with canakinumab: results of a double-blind placebo-controlled randomized withdrawal study. Arthritis Res Ther. 2011;13(6):R202. doi: 10.1186/ar3535.

Kuemmerle-Deschner JB, Hachulla E, Cartwright R, et al (2011a). Two-year results from an open-label, multicentre, phase III study evaluating the safety and efficacy of canakinumab in

patients with cryopyrin-associated periodic syndrome across different severity phenotypes. Ann Rheum Dis. 2011 Dec;70(12):2095-102.

Kuemmerle-Deschner JB, Ramos E, Blank N, Roesler J, et al (2011b). Canakinumab (ACZ885, a fully human IgG1 anti-IL-1β mAb) induces sustained remission in pediatric patients with cryopyrin-associated periodic syndrome (CAPS). Arthritis Res Ther. 2011 Feb 28;13(1):R34.

Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, et al (2009). Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med. 2009 Jun 4;360(23):2416-25.

Livneh A, Langevitz P, Zemer D, et al.(1997) Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 40:1879-85.

Manuel O, Kumar D (2008). QuantiFERON-TB Gold assay for the diagnosis of latent tuberculosis infection. Expert Rev Mol Diagn 8(3):247-55.

Piram M, Frenkel J, Gattorno M, et al (2011). A preliminary score for the assessment of disease activity in hereditary recurrent fevers: results from the AIDAI (Auto-Inflammatory Diseases Activity Index) Consensus Conference. Ann Rheum Dis. 2011 Feb;70(2):309-14. doi: 10.1136/ard.2010.132613.

Piram M, Koné-Paut I, Lachmann HJ, et al (2013). Validation of the Auto-Inflammatory Diseases Activity Index (AIDAI) for ereditary recurrent fever syndromes. Ann Rheum Dis. 2013 Sep 11. doi: 10.1136/annrheumdis-2013-203666.

Ruperto N, Quartier P, Wulffraat N, et al (2012). A phase II, multicenter, open-label study evaluating dosing and preliminary safety and efficacy of canakinumab in systemic juvenile idiopathic arthritis with active systemic features. Arthritis Rheum. 2012 Feb;64(2):557-67. doi: 10.1002/art.33342.

Schwartz GJ, Muñoz A, Schneider MF, et al (2009). New Equations to Estimate GFR in Children with CKD. J Am Soc Nephrol 20: 629–637, 2009. doi: 10.1681/ASN.2008030287

Stojanov S, Kastner DL (2005). Familial autoinflammatory diseases: genetics, pathogenesis and treatment. Curr Opin Rheumatol. 2005 Sep;17(5):586-99.

Ter Haar N, Lachmann H, Ozen S, et al (2012). Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. Ann Rheum Dis. 2012 Jun 29.

Touitou I, Koné-Paut I (2008). Autoinflammatory diseases. Best Pract Res Clin Rheumatol. 2008 Oct;22(5):811-29.

13 Appendix 1: Clinically notable laboratory values and vital signs

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 (>3x ULN) accompanied by elevated bilirubin (> 1.5x ULN, >2x ULN)[1]
4. Any elevations of bilirubin; elevated total bilirubin (TBL) to >2x ULN[1]
5. Any elevations of ALP >1.5x ULN[1]
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 or <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[3]
   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 $10E^9$/L
5. Absolute lymphocytes: <LLN
6. Absolute eosinophils: ≥ 2.5x, ≥ 3x ULN

Urinalysis

a. Protein urine dipstick: ≥ ++

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 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 (> 1.5x ULN, >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 or <85 g/L (patients <16 years of age) or <100 g/L (patients ≥16 years of age)
2. Platelet count[3]
    e. CTC Grade 1: <Lower Limit of Normal (LLN) – 75 x 10^9/L
    f. CTC Grade 2: <75 – 50 x 10^9/L
    g. CTC Grade 3: <50 – 25 x 10^9/L ()
    h. CTC Grade 4: <25x 10^9/L
3. White blood cell count[3]
    e. CTC Grade 1: <LLN – 3 x 10^9/L
    f. CTC Grade 2: <3 – 2 x 10^9/L
    g. CTC Grade 3: <2 – 1 x 10^9/L
    h. CTC Grade 4: <1 x 10^9/L
4. Absolute neutrophils[3]

e. CTC Grade 1: <LLN – 1.5 x 10^9/L
f. CTC Grade 2: <1.5 – 1 x 10^9/L
g. CTC Grade 3: <1 – 0.5 x 10^9/L
h. CTC Grade 4: <0.5 x $10E^9$/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

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
   Normal ranges: LLN = 100, ULN = 115 (2 – 5 years of age), LLN = 110, ULN = 125 (6 – 12 years of age), LLN = 120, ULN = 135 (13 < 18 years of age)
2. Diastolic blood pressure (mmHg): >ULN and increased >20 in change from baseline and <LLN and decreased >20 in change from baseline
   Normal ranges: LLN=65, ULN = 75 (2 – 5 years of age), LLN = 70, ULN = 80 (6 – 12 years of age), LLN = 75, ULN = 85 (13 < 18 years of age)
3. Pulse (bpm): >ULN and increased >20 in change from baseline or <LLN and decreased >20 in change from baseline
   Normal ranges: LLN=80, ULN = 130 (2 – 5 years of age), LLN = 70, ULN = 115 (6 – 12 years of age), LLN = 60, ULN = 100 (13 < 18 years of age)

[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).

14 Appendix 2: Liver event and Laboratory trigger definitions and follow-up requirements

Table 14-1 Liver event and laboratory trigger definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3x ULN < ALT / AST ≤5 x ULN • 1.5x ULN < TBL ≤2 x ULN
LIVER EVENTS	• ALT or AST >5× ULN • ALP >2× ULN (in the absence of known bone pathology) • TBL >2× ULN (in the absence of known Gilbert syndrome) • ALT or AST >3× ULN and INR >1.5 • Potential Hy's Law cases (defined as ALT or AST >3× ULN and TBL >2× ULN [mainly conjugated fraction] without notable increase in ALP to >2× ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST >3× ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity *

* These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Table 14-2 Follow up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	• Complete liver CRF	
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for *more than 2 weeks*, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study drug immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study drug interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

Criteria	Actions required	Follow-up monitoring
*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal [a]Elevated ALT/AST >3 × ULN and TBL >2 × ULN but without notable increase in ALP to >2 × ULN [b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia [c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.		

16 Appendix 4: Level of TB risk

High risk TB patients are defined as follows:

- HIV positive patients
- Patients on concomitant immunosupressants/ immunodeficiency
- Patients who have been in close contact with active TB
- Chest x-ray suggestive of prior TB infection
- Patients with a history of lack of compliance with anti-tuberculosis drug intake for a prior infection/prophylaxis

Moderate risk TB patients are defined as follows:

- Patients living in or coming from countries with a high prevalence of TB
- Healthcare workers
- Patients with diabetes/ silicosis/ chronic renal failure/ malignancies
- Patients exposed to high-risk patients (as described above)
- Infants < 4 years
- Intravenous substance abusers

Low risk TB patients are defined as follows:

- Induration size of 5-9 mm following PPD skin test
- None of the risks listed for high and moderate risk patients