

Global Clinical Development - General Medicine

ACZ885 / Canakinumab

Clinical Trial Protocol CACZ885N2301E2

An extension study of CACZ885N2301, multi-center, open label study of canakinumab in Japanese patients with Periodic Fever Syndromes (TRAPS, HIDS, or crFMF)

Authors:

[REDACTED]

Document type: Clinical Trial Protocol

EUDRACT number: NA

Version number: 00 (Original Protocol)

Clinical trial phase: III

Release date: 03-Jun-2016

Property of Novartis
Confidential

May not be used, divulged, published, or otherwise disclosed
without the consent of Novartis

Clinical Trial Protocol Template Version 3.1 (February 2016)

Table of contents

Table of contents	2
List of tables	5
List of figures	5
List of abbreviations	6
Glossary of terms	8
Protocol summary	9
1 Introduction	11
1.1 Background	11
1.2 Purpose	12
2 Study objectives and endpoints	13
2.1 Primary objective	13
2.2 Secondary objective(s)	13
2.3 Exploratory objectives	13
3 Investigational plan	13
3.1 Study design	13
3.1.1 Screening epoch (Epoch 1)	13
3.1.2 Extension-treatment epoch (Epoch 2)	13
3.2 Rationale for study design	14
3.3 Rationale for dose/regimen, route of administration and duration of treatment	15
3.4 Rationale for choice of comparator	15
3.5 Purpose and timing of interim analyses/design adaptations	15
3.6 Risks and benefits	15
4 Population	16
4.1 Inclusion criteria	16
4.2 Exclusion criteria	16
5 Treatment	18
5.1 Study treatment	18
5.1.1 Investigational and control drugs	18
5.1.2 Additional treatment	18
5.2 Treatment arms	18
5.3 Treatment assignment and randomization	18
5.4 Treatment blinding	18
5.5 Treating the patient	18
5.5.1 Patient numbering	18
5.5.2 Dispensing the study drug	18
5.5.3 Handling of study and additional treatment	18

5.5.4	Instructions for prescribing and taking study treatment.....	19
5.5.5	Permitted dose adjustments and interruptions of study treatment	19
5.5.6	Rescue medication	19
5.5.7	Concomitant medication	20
5.5.8	Prohibited medication	20
5.5.9	Emergency breaking of assigned treatment code.....	20
5.6	Study completion and discontinuation.....	20
5.6.1	Study completion and post-study treatment.....	20
5.6.2	Discontinuation of study treatment	21
5.6.3	Withdrawal of informed consent.....	21
5.6.4	Loss to follow-up	22
5.6.5	Early study termination by the sponsor.....	22
6	Visit schedule and assessments	22
6.1	Information to be collected on screening failures.....	25
6.2	Patient demographics/other baseline characteristics	25
6.3	Treatment exposure and compliance	25
6.4	Efficacy.....	25
6.4.1	Appropriateness of efficacy assessments.....	25
6.5	Safety	25
6.5.1	Physical examination	25
6.5.2	Laboratory evaluations.....	26
6.5.3	Pregnancy and assessments of fertility	26
6.5.4	Appropriateness of safety measurements.....	27
6.6	Other assessments	27
7	Safety monitoring	27
7.1	Adverse events.....	27
7.2	Serious adverse events	29
7.2.1	Definition of SAE	29
7.2.2	SAE reporting.....	30
7.3	Liver safety monitoring	30
7.4	Renal safety monitoring.....	31
7.5	Reporting of study treatment errors including misuse/abuse	31
7.6	Pregnancy reporting.....	32
8	Data review and database management.....	32
8.1	Site monitoring	32
8.2	Data collection	33
8.3	Database management and quality control	33

8.4	Data Monitoring Committee.....	33
8.5	Adjudication Committee.....	34
8.5.1	Infection Adjudication Committee.....	34
8.5.2	Malignancy Adjudication Committee.....	34
9	Data analysis.....	34
9.1	Analysis sets.....	34
9.2	Patient demographics and other baseline characteristics.....	34
9.3	Treatments.....	34
9.4	Analysis of the primary variable(s).....	34
9.4.1	Variable(s).....	34
9.4.2	Statistical model, hypothesis, and method of analysis.....	34
9.4.3	Handling of missing values/censoring/discontinuations.....	35
9.4.4	Sensitivity analyses.....	35
9.5	Analysis of secondary variables.....	35
9.5.1	Efficacy variables.....	35
9.5.2	Safety variables.....	35
9.5.3	Resource utilization.....	35
9.5.4	Pharmacokinetics.....	35
9.5.5	DNA.....	35
9.5.6	Biomarkers.....	35
9.5.7	PK/PD.....	35
9.6	Analysis of exploratory variables.....	36
9.7	Interim analyses.....	36
9.8	Sample size calculation.....	36
10	Ethical considerations.....	36
10.1	Regulatory and ethical compliance.....	36
10.2	Informed consent procedures.....	36
10.3	Responsibilities of the investigator and IRB/IEC.....	37
10.4	Publication of study protocol and results.....	37
10.5	Quality Control and Quality Assurance.....	37
11	Protocol adherence.....	37
11.1	Protocol amendments.....	38
12	References.....	39
13	Appendix 1: Clinically notable laboratory values.....	41
14	Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements.....	44
15	Appendix 3: Specific Renal Alert Criteria and Actions.....	46

List of tables

Table 5-1	Prohibited treatment	20
Table 6-1	Assessment schedule	23
Table 7-1	Guidance for capturing the study treatment errors including misuse/abuse	32
Table 14-1	Liver Event and Laboratory Trigger Definitions	44
Table 14-2	Follow Up Requirements for Liver Events and Laboratory Triggers ...	44
Table 15-1	Specific Renal Alert Criteria and Actions.....	46

List of figures

Figure 3-1	Study design	14
------------	--------------------	----

List of abbreviations

AE	Adverse Event
Alb	albumin
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMD	aged-related macular degeneration
AST	Aspartate Aminotransferase
CAN	Canakinumab
CAPS	Cryopyrin Associated Periodic Syndrome
CFR	US Code of Federal Regulations
CRF	Case Report/Record Form (paper or electronic)
crFMF	colchicine resistant Familial Mediterranean Fever
CPO	Country Pharma Organization
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
ECG	Electrocardiogram
FMF	Familial Mediterranean Fever
GCP	Good Clinical Practice
HIDS	Hyper IgD Syndrome
IB	Investigator Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL	interleukin
i.v.	intravenous
IRB	Institutional Review Board
LFT	Liver function test
MedDRA	Medical dictionary for regulatory activities
MKD	Mevalonate Kinase Deficiency
OC/RDC	Oracle Clinical/Remote Data Capture
PGA	Physician's Global Assessment of Disease Activity
PSW	premature subject withdrawal

q4w	Every 4 weeks
q8w	Every 8 weeks
SAE	Serious Adverse Event
SJIA	systemic juvenile idiopathic arthritis
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total bilirubin
TD	Study Treatment Discontinuation
TRAPS	TNF-receptor Associated Periodic Syndrome
WHO	World Health Organization

Glossary of terms

Cohort	A specific group of patients/subjects fulfilling certain criteria
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. 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
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.”
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
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) or background therapy
Study Treatment Discontinuation (TD)	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
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
Withdrawal of consent	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	CACZ885N2301E2
Title	An extension study of CACZ885N2301, multi-center, open label study of canakinumab in Japanese patients with Periodic Fever Syndromes (TRAPS, HIDS, or crFMF)
Brief title	An extension study of safety of canakinumab in Japanese patients with Periodic Fever Syndromes
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	<p>This is an open label extension study to 'A randomized, double-blind, placebo controlled study of canakinumab in patients with Periodic Fever Syndromes (TRAPS, HIDS, or crFMF), with subsequent randomized withdrawal/ dosing frequency reduction and open-label long term treatment epochs' (CACZ885N2301).</p> <p>This extension study offers the opportunity for patients who completed Epoch 4 of the preceding CACZ885N2301 study to continue to be treated with ACZ885 until approval in Japan of the drug in Periodic Fever Syndromes or until development of ACZ885 in Periodic Fever Syndromes is suspended.</p>
Primary Objective	The primary objective of this study is to evaluate safety and tolerability of ACZ885 in this extension study.
Secondary Objectives	Not applicable.
Study design	<p>Japanese patients are allowed to enter this extension study after completion of Epoch 4 (an open-label treatment epoch) in CACZ885N2301 study. This study consists of two study epochs (Screening epoch and Extension-treatment epoch). This study will be continued until approval in Japan or the discontinuation of the development of the drug in Periodic Fever Syndromes.</p> <p>In this study, all patients will receive the same dose and regimen as administered at the end of study CACZ885N2301 consisting of 1 or 2 subcutaneous injections every 4 or 8 weeks. Safety will be evaluated every 8 weeks.</p>
Population	Completed Epoch 4 of the CACZ885N2301 study in Japan before the approval of canakinumab in Japan.
Inclusion criteria	<ul style="list-style-type: none"> Completed Epoch 4 of the CACZ885N2301 study in Japan before the approval of canakinumab in Japan. Before or at Visit 1, written informed consent must be obtained before any assessment is performed from those ≥ 20 years of age. Parent or legal guardian's written informed consent and child's assent, if appropriate, are required before any assessment is performed for patients < 20 years of age.

Exclusion criteria	<ul style="list-style-type: none"> • Any conditions or significant medical problems in which the investigator judges the patient should not enter this extension study. • Pregnant or nursing (lactating) women • Female adolescents (\leq 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. • 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.
Investigational and reference therapy	<ul style="list-style-type: none"> • Canakinumab solution for injection in vial which contains 150 mg canakinumab in 1 mL solution
Efficacy assessments	<ul style="list-style-type: none"> • Not applicable.
Safety assessments	<ul style="list-style-type: none"> • Physical examination • Laboratory evaluations • Pregnancy and assessments of fertility
Other assessments	<ul style="list-style-type: none"> • No additional tests will be performed.
Data analysis	<p>Due to a very limited number of patients enrolled, specific listings will be produced for reporting purpose, and no statistical analysis will be performed.</p> <p>Primary variable is adverse events.</p> <p>Adverse events will be coded using the MedDRA dictionary that provides the primary system organ class and preferred term information.</p> <p>A listing will be presented to display individual adverse events reported</p>
Key words	<p>Canakinumab, interleukin-1, Periodic Fevers Syndrome, TRAPS, HIDS, crFMF, auto-inflammatory diseases, extension study</p>

1 Introduction

1.1 Background

Periodic Fever Syndromes, 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)/ Mevalonate Kinase Deficiency (MKD) and Familial Mediterranean Fever (FMF) ([Drenth and van der Meer 2001](#), [Goldbach-Mansky 2012](#), [Stojanov and Kastner 2005](#), [Touitou and Koné-Paut 2008](#)). There are currently no approved treatments for TRAPS, HIDS/MKD 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 2013](#), [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 ([Hoffman and Simon 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-1 β (IL-1 β) antibody of the IgG1/ κ isotype. Canakinumab is designed to bind to human IL-1 β blocking the interaction of this cytokine to its receptors, thus functionally neutralizing the bioactivity of this cytokine, IL-1 β is recognized as one of the principal pro inflammatory cytokines in a variety of inflammatory conditions ([Dinarello et al 2012](#)).

As of 30th June 2015, approximately 10,510 patients (578 of pediatric age) received ILARIS treatment in Novartis-sponsored investigational clinical trials in a wide spectrum of IL-1 β driven diseases such as: 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 6,922.7 patient-treatment-years (Investigator Brochure Edition 14.0).

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](#), [Koné-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 Periodic Fever Syndromes ([Gattorno et al 2012](#), [Gul et al 2012](#)).

In over 70 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-1 β .

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/MKD 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 PoC studies, using various dosing regimens, results of the primary endpoint showed rates of responses $\geq 85\%$ 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. Results from the primary N2301 study Epoch 2 have formed the basis of global regulatory filing for the treatment of the studied indications with canakinumab. This extension study is planned to offer the opportunity to continue the treatment with ACZ885 until approval in Japan or the discontinuation of the development of the drug in Periodic Fever Syndromes. Eligible patients are those in Japan who completed Epoch 4 of CACZ885N2301 study.

1.2 Purpose

This is an open label extension study to ‘A randomized, double-blind, placebo controlled study of canakinumab in patients with Periodic Fever Syndromes (TRAPS, HIDS, or crFMF), with subsequent randomized withdrawal/ dosing frequency reduction and open-label long term treatment epochs’ (CACZ885N2301). The primary objective of the preceding CACZ885N2301 study was 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.

This extension study offers the opportunity for patients who completed Epoch 4 of the preceding CACZ885N2301 study to continue to be treated with ACZ885 until approval in Japan of the

drug in Periodic Fever Syndromes or until development of ACZ885 in Periodic Fever Syndromes is suspended.

2 Study objectives and endpoints

2.1 Primary objective

The primary objective of this study is to evaluate safety and tolerability of ACZ885 in this extension study.

2.2 Secondary objective(s)

Not applicable.

2.3 Exploratory objectives

Not applicable.

3 Investigational plan

3.1 Study design

Japanese patients are allowed to enter this extension study after completion of Epoch 4 (an open-label treatment epoch) in CACZ885N2301 study. This study consists of two study epochs (Screening epoch and Extension-treatment epoch). This study will be continued until approval in Japan or the discontinuation of the development of the drug in Periodic Fever Syndromes.

In this study, all patients will receive the same dose and regimen as administered at the end of study CACZ885N2301 consisting of 1 or 2 subcutaneous injections every 4 or 8 weeks. Safety will be evaluated every 8 weeks.

3.1.1 Screening epoch (Epoch 1)

At Visit 1, patients will be assessed for eligibility ([Section 4](#)) for study participation after completion of Epoch 4 of the CACZ885N2301 study.

Visit 1 of this extension study and Visit 399 of the CACZ885N2301 study are conducted on the same day.

3.1.2 Extension-treatment epoch (Epoch 2)

Patients who meet entry criteria at Visit 1 will enter the extension-treatment epoch (epoch 2). Since eligible patients initiate the extension-treatment epoch on the same day of screening, their first two visits (Visit 1 and Visit 101) can be on the same day.

Patients will continue the study drug based on the final dose and regimen administered at the end of the CACZ885N2301 study. All patients will receive 1 or 2 ACZ885 subcutaneous injections every 4 or 8 weeks. Stepwise up-titration up to a dosing regimen of ACZ885 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) every 4 weeks (q4w) will be allowed. In case of re-

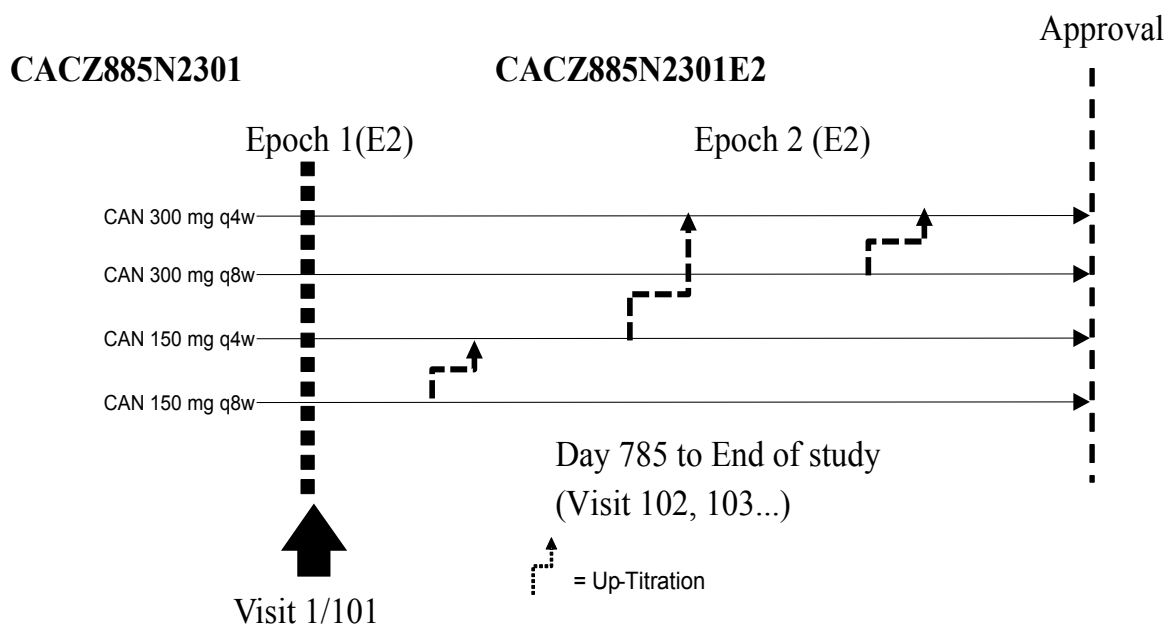
flare [Physician’s global assessment of disease activity (PGA) ≥ 2 AND CRP ≥ 30 mg/L], patients will be allowed to increase the dose as follows and accordingly to the same up-titration scheme in study CACZ885N2301: If flare occurs at the last visit (V399) or visit between V309 and V399 of CACZ885N2301 study, up-titration will be allowed at visit 101.

- If patients receive ACZ885 150 mg (or 2 mg/kg for patients weighing ≤ 40 kg) every 8 weeks (q8w), they will increase the dose to ACZ885 150 mg q4w.
- If patients receive ACZ885 150 mg (or 2 mg/kg for patients weighing ≤ 40 kg) q4w, they will increase the dose to ACZ885 300 mg q4w.
- If patients receive ACZ885 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) q8w, they will increase the dose to ACZ885 300 mg q4w.

If flare occurs at the last visit (V399) it will be recorded in the CACZ885N2301 study. Safety will be evaluated every 8 weeks in the extension- treatment epoch (epoch 2). Patients receiving ACZ885 q4w or up-titrated to q4w administration, will come back every 4 weeks for unscheduled visits in addition to the scheduled visits as indicated in [Table 6-1](#)

For all patients, a safety follow-up visit should be conducted (e.g. by telephone) 30 days after study treatment discontinuation (TD)/ premature subject withdrawal (PSW), or 8 weeks after last injection of investigational drug, whichever is later ([Table 6-1](#)).

Figure 3-1 Study design



All patients will receive the same dose and regimen as administered at the end of study CACZ885N2301.

3.2 Rationale for study design

This extension study offers the opportunity to Japanese patients who completed Epoch 4 of the CACZ885N2301 study to be treated with ACZ885 until approval of the drug is granted in Japan or the development of the drug is suspended in Periodic Fever Syndromes. Therefore, an open

label design has been selected. The visit schedule follows on from the Epoch 4 of CACZ885N2301 study.

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

Since this is an extension study of the CACZ885N2301 study, patients will receive the study drug with a starting dose based on final dose regimen received in the CACZ885N2301 study. Study duration will continue until approval of the drug is granted in Japan or the development of the drug is suspended in Periodic Fever Syndromes.

3.4 Rationale for choice of comparator

Not applicable.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

In TRAPS, HIDS/MKD 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 2013](#), [Hoffman and Simon 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/MKD.

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/MKD, 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/MKD

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. And the result from the CACZ885N2301 study Epoch 2 data, which is placebo-controlled Phase 3 confirmatory study with canakinumab in these 3 indications, has shown the overall favorable benefit-risk profile.

4 Population

This study population will be Japanese patients who completed Epoch 4 of the CACZ885N2301 study.

4.1 Inclusion criteria

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

1. Completed Epoch 4 of the CACZ885N2301 study in Japan before the approval of canakinumab in Japan.
2. Before or at Visit 1, written informed consent must be obtained before any assessment is performed from those ≥ 20 years of age. Parent or legal guardian's written informed consent and child's assent, if appropriate, are required before any assessment is performed for patients < 20 years of age.

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/subjects.

1. Any conditions or significant medical problems in which the investigator judges the patient should not enter this extension study.
2. Pregnant or nursing (lactating) women
3. 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 6.5.3](#).
4. 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 stable 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 Study treatment

5.1.1 Investigational and control drugs

Novartis will provide the following investigational treatment:

- Canakinumab solution for injection in vial which contains 150 mg canakinumab in 1 mL solution

5.1.2 Additional treatment

No additional treatment beyond investigational drug and control drug are included in this trial.

5.2 Treatment arms

Patients will continue the study drug based on final dose regimen received (e.g. one of the following regimen) in the CACZ885N2301 study.

- ACZ885 150 mg (or 2 mg/kg for patients weighing ≤ 40 kg) q4w
- ACZ885 150 mg (or 2 mg/kg for patients weighing ≤ 40 kg) q8w
- ACZ885 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) q4w
- ACZ885 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) q8w

5.3 Treatment assignment and randomization

This is an open label study.

5.4 Treatment blinding

Not applicable.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Patient numbering

Patient numbers used in the preceding CACZ885N2301 study will be used continuously for those patients enrolling in this extension study.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study 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 study treatment must 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 and Lot number for the study treatment but no information about the patient.

The investigator must maintain an accurate record of the shipment and dispensing of study 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 study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study 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 additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study 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 provided in the CACZ885N2301 study.

All patients will receive 1 or 2 s.c. injections every 4 or 8 weeks based on the final dose regimen received in the CACZ885N2301 study and depending upon criteria met for up-titration ([Section 3.1.2](#)) until TD/ PSW.

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

5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational treatment dose adjustments and/or interruptions other than those detailed in [Section 3.1.2](#) are not permitted.

All dose changes must be recorded on the Dosage Administration Record CRF.

5.5.6 Rescue medication

Standard doses of NSAIDs and corticosteroids can be used as needed basis to treat the signs and symptoms of TRAPS, HIDS/MKD or crFMF during acute flares at the discretion of the investigator.

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

5.5.7 Concomitant medication

The investigator must 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 is enrolled into this extension study must be recorded in the concomitant medications / significant non-drug therapies eCRF.

Each concomitant drug must be individually assessed against all prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before allowing a new medication to be started.

5.5.8 Prohibited medication

Use of the treatments displayed in [Table 5-1](#) is NOT allowed after Screening. Once canakinumab is approved for Periodic Fever Syndromes (TRAPS, HIDS/MKD, or crFMF), it can be used according to the package insert.

Table 5-1 Prohibited treatment

Medication	Action to be taken
Anakinra	Investigational treatment to be discontinued ²
Riloncept, 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
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 Emergency breaking of assigned treatment code

This is an open label study.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit of extension- treatment epoch planned in the protocol.

For all patients a safety follow-up visit should be conducted (e.g. by telephone) 30 days after last visit 199 or TD/PSW, or 8 weeks after last injection of investigational drug, whichever is later. 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.

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Emergence of the following adverse events:
 - a. Absolute QTcF > 500 msec, confirmed by repeat electrocardiogram (ECG) measurements
 - b. Serious infections combined with neutropenia Common Toxicity Criteria (CTC) grades ≥ 1 (ANC < $2.0 \times 10^9/L$)
 - c. CKD as per NKF stages ≥ 4 : eGFR ≤ 29 mL/min/1.73 m²
 - d. Confirmed diagnosis of latent or active Tuberculosis
 - e. Onset of any malignancy
- Any of the following laboratory abnormalities:
 - a. Neutropenia CTC Grades ≥ 2 : ANC < $1.5 \times 10^9/L$
 - b. Thrombocytopenia CTC Grade 4: Platelets < $10.0 \times 10^9/L$
- 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

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. The patient should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation visit. Treatment discontinuation visit assessments detailed in the "treatment discontinuation visit" in [Table 6-1](#) should be completed and recorded in the eCRF. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage Administration eCRF.

5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as 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

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table.

5.6.4 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or 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 cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit would have occurred.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as 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 lists all of the assessments and indicates with an "x" when the visits are performed.

At a minimum, patients will be contacted for safety evaluations and a follow-up visit or phone call for Serious Adverse Event (SAE) must be performed 30 days following study 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

Epoch	Screening (Epoch 1)	Extension- treatment (Epoch 2)			Safety follow-up
	1#	101#	102, 103....	199 and TD and/or PSW ⁶	
Week (Relative to Baseline of core study)	113	113	121, 129....		
Day	785	785	841, 897....		PSW +30 or 8 weeks after last injection
Informed consent	X				
Demography	X				
Inclusion/Exclusion Criteria	X				
Relevant medical history/ current medical conditions	X				
Prior and concomitant medications (<i>including vaccination status</i>) *	X	X	X	X	
Surgical and medical procedures*	X	X	X	X	
Disease Diagnosis	X				
Disease characteristics	X				
Pregnancy test –urinalysis (for females of child bearing potential) *		S		S	
Physical examination ^{*,7}		S	S	S	
Weight ^{2,3,7}		S	S		
PGA ^{2,4,7}		S	S		
Hematology (local Lab) *		X	X	X	
Blood chemistry (local Lab) *		X	X	X	
CRP (local Lab) ^{2,5,7}		S	S		
Administration of open-label treatment ¹		X	X		
Adverse events*	X	X	X	X	
Local tolerability ^{*,7}		S	S	S	
Screening phase disposition form	X				
Study phase completion form*				X	
Follow-up visit or phone call for SAEs*					S

TD = Study treatment discontinuation; PSW = Premature subject withdrawal

X = assessment to be recorded on clinical data base

S = assessment to be recorded on source documentation only

*These assessments are also to be conducted for patients who discontinue

Visit 1 of this extension study and Visit 399 of the CACZ885N2301 study are conducted on the same day. Visit 1 and Visit 101 can be on the same day

1. Patients receiving ACZ885 q4w or up-titrated to q4w administration will come back every 4 weeks for unscheduled visits at Day 813, Day 869 and so forth in addition to the scheduled visits

2. These assessments are source documentation only and will not be entered into the CRF, because they will be used only for dose adjustment or judgement of up-titration due to flare. Flare is defined as simultaneous occurrence of a clinical flare and a serological flare defined as follows:

- PGA \geq 2 (clinical flare)

- CRP \geq 30 mg/L (serological flare)

3. Body weight to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes

4. The PGA (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

5. 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.

6. After canakinumab is approved for Periodic Fever Syndromes (TRAPS, HIDS, or crFMF) in Japan, all subjects who continue study treatment at the timing will be expected to perform V199 evaluation approximately 8 weeks after their most recent assessment visit, and then will enter the safety follow-up period.

7. If V 101 of this extension study and V 399 of the CACZ885N2301 study are conducted on the same day, Physical exam, PGA, CRP, weight, local tolerability will be assessed only one time.

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 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: year of birth, age, sex, race, ethnicity, 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](#).

6.3 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

Not applicable.

6.4.1 Appropriateness of efficacy assessments

This extension study is planned to offer the opportunity to continue the treatment with ACZ885 until approval in Japan or the discontinuation of the development of the drug in Periodic Fever Syndromes, for the patients who completed Epoch 4 of CACZ885N2301 study. Therefore, efficacy assessment is out of scope.

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 5.6.2](#).

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 short physical exam will include the examination of general appearance and vital signs.

A complete physical examination or a short physical exam (investigator judges which physical examination is appropriate) will be at all visits. Physical examination at Visit 1/101 will not be necessary in this study when it was conducted at Visit 399 in the preceding N2301 study.

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 Laboratory evaluations

All laboratory evaluations will be conducted locally. Clinically notable laboratory findings are defined in [Appendix 1](#).

6.5.2.1 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.

Hematology samples are to be collected at visits shown in [Table 6-1](#).

6.5.2.2 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), uric acid and CRP.

Clinical chemistry samples are to be collected at visits shown [Table 6-1](#).

6.5.3 Pregnancy and assessments of fertility

6.5.3.1 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 pregnancy test must be performed at the local lab as shown in [Table 6-1](#).

If a pregnancy test is positive, the patient must be discontinued from the trial and followed up according to [Section 5.6.2](#).

6.5.3.2 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 #4 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.

6.5.3.3 Female pediatric patients (< 12 years)

No pregnancy tests are required. Pregnancy test will be conducted if investigator judges to be necessary.

6.5.4 Appropriateness of safety measurements

The safety assessments selected are appropriate because subjects who completed assessment of long-term safety in the core study of N2301 will enter in the study in order to continue receiving study drug until approval in Japan.

6.6 Other assessments

No additional tests will be performed on patients/subjects entered into this study.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., 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 until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, 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 must 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 laboratory and other test abnormalities are included in [Appendix 1](#).

Adverse events must be recorded in the Adverse Events 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 study treatment
 - Yes
 - No
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See [Section 7.2](#) for definition of SAE) and which seriousness criteria have been met.
- action taken regarding [investigational] treatment
All adverse events must be treated appropriately. Treatment may include one or more of the following:
 - a. no action taken (e.g. further observation only)
 - b. [investigational] treatment dosage increased/reduced
 - c. [investigational] treatment interrupted/withdrawn
 - d. concomitant medication or non-drug therapy given
 - e. non-drug therapy given
 - f. patient hospitalized/patient's hospitalization prolonged (see [Section 7.2](#) for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must 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). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must 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 must 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 adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical condition(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:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
 - 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
 - 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
 - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

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 it were more severe (please refer to Annex IV, ICH-E2D Guideline).

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 or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

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

7.2.2 SAE reporting

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to the study drug complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

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 study 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 study 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 (irrespective of whether classified/reported as (S)AE):

- 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 AE CRF pages

Please refer to [Table 14-1 in 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 of Appendix 2](#) 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 in Appendix 2](#).

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

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. The event must be recorded on the Adverse Event section of the CRF.

7.4 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

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

Every renal laboratory trigger or renal event as defined in [Table 15-1 in Appendix 3](#) should be followed up by the investigator or designated personnel at the trial site as summarized in [Appendix 3](#). The event must be recorded on the Adverse Event section of the CRF.

7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes,	Yes, even if not associated with an SAE

7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent 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 must 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 study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on an 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 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 Contract Research Organization (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.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

8.5.1 Infection Adjudication Committee

Not applicable.

8.5.2 Malignancy Adjudication Committee

Not applicable.

9 Data analysis

Due to a very limited number of patients enrolled, specific listings will be produced for reporting purpose, and no statistical analysis will be performed.

9.1 Analysis sets

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

The **Safety Set** will consist of all patients receiving at least a single dose of study medication in the extension study.

9.2 Patient demographics and other baseline characteristics

Demographic and baseline characteristics will be listed.

Any significant prior or active medical condition at the time of signing informed consent will be also listed.

9.3 Treatments

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

Rescue medication will be also listed.

9.4 Analysis of the primary variable(s)

Analysis of the primary variable will be performed on the Safety set.

9.4.1 Variable(s)

Primary variable is adverse events.

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

A listing will be presented to display individual adverse events reported.

9.4.2 Statistical model, hypothesis, and method of analysis

Not applicable.

9.4.3 Handling of missing values/censoring/discontinuations

Not applicable.

9.4.4 Sensitivity analyses

Not applicable.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Not applicable.

9.5.2 Safety variables

All safety evaluations will be performed on the Safety set.

9.5.2.1 Adverse events

Adverse event is primary variable.

9.5.2.2 Weight

Not applicable.

9.5.2.3 Vital signs

Not applicable.

9.5.2.4 Laboratory evaluations

Laboratory evaluations will be listed by patient.

9.5.3 Resource utilization

Not applicable.

9.5.4 Pharmacokinetics

Not applicable.

9.5.5 DNA

Not applicable.

9.5.6 Biomarkers

Not applicable.

9.5.7 PK/PD

Not applicable.

9.6 Analysis of exploratory variables

Not applicable.

9.7 Interim analyses

Not applicable.

9.8 Sample size calculation

Patients who completed Epoch 4 of the preceding CACZ885N2301 study in Japan will be eligible for entry into this extension study. Therefore the maximum number of patients is 10.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed 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 must 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.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

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

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance (CQA), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

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 is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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.

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/subjects 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](#) Safety Monitoring must be followed.

12 References

References are available upon request

Aksentijevich I and Kastner DL (2011) Genetics of monogenic autoinflammatory diseases: past successes, future challenges. *Nat Rev Rheumatol*; 7(8):469-78.

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*; 11(8):633-52.

Drenth JP and van der Meer JW (2001) Hereditary periodic fever. *N Engl J Med*; 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*; 64(10) 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*; 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*; 64(10) S322 abstract 750.

Hoffman HM and Simon A (2009) Recurrent febrile syndromes: what a rheumatologist needs to know. *Nat Rev Rheumatol*; 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*; 13(6):R202.

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*; 70(12):2095-102.

Kuemmerle-Deschner JB, Ramos E, Blank N, et al (2011b) Canakinumab (ACZ885, a fully human IgG1 anti-IL-1 β mAb) induces sustained remission in pediatric patients with cryopyrin-associated periodic syndrome (CAPS). *Arthritis Res Ther*; 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*; 360(23):2416-25.

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*; 70(2):309-14.

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*; 64(2):557-67.

Schwartz GJ, Munoz A, Schneider MF, et al (2009) New Equations to Estimate GFR in Children with CKD. *J Am Soc Nephrol*; 20(3):629-37.

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

Ter Haar N, Lachmann H, Ozen S, et al (2013) Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. *Ann Rheum Dis*; 72(5):678-85.

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

13 Appendix 1: Clinically notable laboratory values

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

Hematology

1. Hemoglobin: ≥ 20 g/L decrease from baseline or < 100 g/L
2. Platelet count ³
 - a. CTC Grade 1: $< \text{Lower Limit of Normal (LLN)} - 75 \times 10^9/\text{L}$
 - b. CTC Grade 2: $< 75 - 50 \times 10^9/\text{L}$
 - c. CTC Grade 3: $< 50 - 25 \times 10^9/\text{L}$
 - d. CTC Grade 4: $< 25 \times 10^9/\text{L}$
3. White blood cell count ³
 - a. CTC Grade 1: $< \text{LLN} - 3 \times 10^9/\text{L}$
 - b. CTC Grade 2: $< 3 - 2 \times 10^9/\text{L}$
 - c. CTC Grade 3: $< 2 - 1 \times 10^9/\text{L}$
 - d. CTC Grade 4: $< 1 \times 10^9/\text{L}$
4. Absolute neutrophils ³
 - a. CTC Grade 1: $< \text{LLN} - 1.5 \times 10^9/\text{L}$
 - b. CTC Grade 2: $< 1.5 - 1 \times 10^9/\text{L}$
 - c. CTC Grade 3: $< 1 - 0.5 \times 10^9/\text{L}$
 - d. CTC Grade 4: $< 0.5 \times 10^9/\text{L}$
5. Absolute lymphocytes: $< \text{LLN}$
6. Absolute eosinophils: ≥ 2.5 x, ≥ 3 x ULN

Urinalysis

- a. Protein urine dipstick: $\geq ++$

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

Hematology

1. Hemoglobin: \geq 20 g/L decrease from baseline or < 85 g/L (patients < 16 years of age) or < 100 g/L (patients \geq 16 years of age)
2. Platelet count ³
 - e. CTC Grade 1: < Lower Limit of Normal (LLN) – 75 x 10⁹/L
 - f. CTC Grade 2: < 75 – 50 x 10⁹/L
 - g. CTC Grade 3: < 50 – 25 x 10⁹/L
 - h. CTC Grade 4: < 25 x 10⁹/L
3. White blood cell count ³
 - e. CTC Grade 1: < LLN – 3 x 10⁹/L
 - f. CTC Grade 2: < 3 – 2 x 10⁹/L
 - g. CTC Grade 3: < 2 – 1 x 10⁹/L
 - h. CTC Grade 4: < 1 x 10⁹/L
4. Absolute neutrophils ³
 - e. CTC Grade 1: < LLN – 1.5 x 10⁹/L
 - f. CTC Grade 2: < 1.5 – 1 x 10⁹/L
 - g. CTC Grade 3: < 1 – 0.5 x 10⁹/L
 - h. CTC Grade 4: < 0.5 x 10⁹/L
5. Absolute lymphocytes: < LLN
6. Absolute Eosinophils: \geq 1.1 x ULN, \geq 0.45 x 10⁹/L

Urinalysis

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

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

² Cockcroft-Gault formula (Men): $\text{CrCl (mL/min)} = [((140 - \text{age (years)}) \times \text{weight (kg)}) / (\text{serum creatinine } (\mu\text{mol/L}) / 88.4) (\text{mg/dL}) \times 72]$

² Cockcroft-Gault formula (Women): $\text{CrCl (mL/min)} = [((140 - \text{age (years)}) \times \text{weight (kg)}) / (\text{serum creatinine } (\mu\text{mol/L}) / 88.4) (\text{mg/dL}) \times 72] \times 0.85$

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:

$\text{CrCl (mL/min/1.73 m}^2) = [0.413 \times \text{length (cm)} / (\text{serum creatinine mg/dl})]$ (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	$3 \times \text{ULN} < \text{ALT} / \text{AST} \leq 5 \times \text{ULN}$ $1.5 \times \text{ULN} < \text{TBL} \leq 2 \times \text{ULN}$
LIVER EVENTS	ALT or AST $> 5 \times \text{ULN}$ ALP $> 2 \times \text{ULN}$ (in the absence of known bone pathology) TBL $> 2 \times \text{ULN}$ (in the absence of known Gilbert syndrome) ALT or AST $> 3 \times \text{ULN}$ and INR > 1.5 Potential Hy's Law cases (defined as ALT or AST $> 3 \times \text{ULN}$ and TBL $> 2 \times \text{ULN}$ [mainly conjugated fraction] without notable increase in ALP to $> 2 \times \text{ULN}$) Any clinical event of jaundice (or equivalent term) ALT or AST $> 3 \times \text{ULN}$ 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 treatment immediately Hospitalize, if clinically appropriate Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and γ GT until resolution ^c (frequency at investigator discretion)
ALT or AST		
$> 8 \times \text{ULN}$	Discontinue the study treatment immediately Hospitalize if clinically appropriate Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and γ GT until resolution ^c (frequency at investigator discretion)
$> 3 \times \text{ULN}$ and INR > 1.5	Discontinue the study treatment immediately Hospitalize, if clinically appropriate Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and γ GT until resolution ^c (frequency at investigator discretion)
> 5 to $\leq 8 \times \text{ULN}$	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	ALT, AST, TBL, Alb, PT/INR, ALP and γ GT until resolution ^c (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms ^b	Discontinue the study treatment immediately Hospitalize if clinically appropriate Establish causality	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	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	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 treatment immediately Hospitalize the patient Establish causality	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 treatment interruption or discontinuation Hospitalization if clinically appropriate Establish causality	Investigator discretion

^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.

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific Renal Alert Criteria and 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 study treatment 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 study treatment interruption / or discontinuation
New dipstick glycosuria ≥ 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:	
<p><u>Document contributing factors in the CRF:</u> co-medication, other co-morbid conditions, and additional diagnostic procedures performed</p> <p>Monitor patient regularly (frequency at investigator's discretion) until either:</p> <ul style="list-style-type: none"> Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months. 	