NOVARTIS

Clinical Development

[ACZ885/canakinumab]

Clinical Trial Protocol CACZ885GFR01 / NCT02334748

A French open-label extension study of canakinumab in patients who participated in international phase III studies CACZ885G2301E1 or CACZ885G2306 in Systemic Juvenile Idiopathic Arthritis and CACZ885N2301 in Hereditary Periodic Fevers (TRAPS, HIDS, or crFMF).

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List of abbreviations

AE	Adverse Event
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
DS&E	Drug Safety & Epidemiology
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
SAE	Serious Adverse Event

Glossary of terms

Assessment	A procedure used to generate data required by the study
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Subject Number	A number assigned to each patient who enrolls into the study
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all investigational/study treatment administration and all assessments (including follow-up)
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

Amendment 5

Changes to the protocol are related to the following sections:

- Section 4.1. inclusion criteria

  The current version of inclusion criteria stipulates that *"patients who have completed the international CACZ885G2306 study and who successfully withdrew canakinumab treatment per protocol but with a disease relapse within one year from the End of study visit will be allowed to participate in CACZ885GFR01 study"*.

The purpose of the change is to enable these patients who experienced a relapse to be included in the local extension study CACZ885GFR01 with no time limitation after the end of study visit.

Canakinumab is still not commercially available in France in the SJIA (Systemic Juvenile Idiopathic Arthritis) indication at the date of the amendment 5. The inclusion in the local extension study is the only option to treat these patients and to resume canakinumab, when medically justified.

- Section 5. Treatment

For patients previously included in study CACZ885G2301E1 (SJIA), the option to interrupt canakinumab after a prolonged remission according to the investigators judgment has been added.

Every patient withdrawn from CACZ885GFR01 study due to a remission will be allowed to resume canakinumab in case of relapse and will be followed up again in the study.

- Section 5.1.1 . Investigational treatment

Novartis has been supplying the open-label investigational drug (canakinumab) under the form of a lyophilisate in vial. A marketing authorization has been granted in February 2017 by the European

Commission for canakinumab as a solution for injection.

If necessary (for logistic reasons), Novartis may supply one or the other pharmaceutical form for the trial. There will not be any change for the patient in the way the medication is administered (subcutaneously).

Amendment 4

The purpose of amendment 4 is to modify the paragraph 4.1 (Inclusion criteria), to take into account particular situations of some patients who have been included in international phase III study CAC885G2306, to enable them to be included in the local extension study CACZ885GFR01. This amendment is aiming:

- to extend the period to allow inclusion of patients for the patients who have completed the international CACZ885G2306 study and who successfully withdrew canakinumab treatment per protocol but with a disease relapse in the following months. After amendment 4, patients who will relapse **within one year from the End of study visit** (instead of within one year from end of treatment) will be allowed to participate in CACZ885GFR01 study.

- to add a new inclusion criteria to take into account the specific situation of the patients of CACZ885G2306 study, not randomized (after randomization closure), and who, according to the international protocol, are supposed to remain at 4 mg/kg every 4 weeks until the end of the study. After a stable and prolonged remission in part II the investigators may propose to reduce the canakinumab dose in the interest of the patients as proposed in current practice (but not allowed in the current protocol). These patients (3 to 5 patients), will be withdrawn from CACZ885G2306 study and will be allowed to participate in CACZ885GFR01 study to continue canakinumab treatment.

Amendment 3

The purpose of amendment 3 is to open the recruitment of study CACZ885GFR01 to patients who will complete:

- the phase III international study CACZ885N2301 designed to assess efficacy and tolerability of canakinumab in patients suffering from 3 rare Hereditary Periodic Fevers [TRAPS (TNF receptor associated periodic syndrome), HIDS (hyperimmunoglobulinemia D syndrome) or crFMF (colchicine resistant Familial Mediterranean Fever)],
- or the phase III international study CACZ885G2306 designed to assess 2 different canakinumab taper regimens in patients suffering from SJIA (Systemic Juvenile Idiopathic Arthritis) with clinical remission (inactive disease for at least 24 continuous weeks) on canakinumab treatment.

The objective is to provide continuous treatment to these patients once CACZ885N2301 and CACZ885G2306 are completed and until this medication is commercially available in France for these new indications.

Taking into account the status of these ongoing studies at the date of May 2016, we may anticipate that a maximum of 8 patients included in CACZ885N2301 (within 4 French centers) may be included in CACZ885GFR01 from November 2016 and that a maximum of 21 patients included in CACZ885G2306 (within 3 French centers) from October 2016.

The last visit of study CACZ885N2301 will be the first visit of study CACZ885GFR01. Patients will continue on their last dosing regimen of the open-label long term treatment epochs (Epochs 4) considered to constitute the lowest clinically efficacious doses to maintain clinical efficacy in individual patients. Patients may receive an up-titration if they re-flare (maximum dose of 300 mg/ 4 mg/kg for patients weighing ≤40 kg) q4w.

The follow-up of patients with Hereditary Periodic Fever will be the same as the one for patients with SJIA.

The last visit of study CACZ885G2306 will also be the first visit of study CACZ885GFR01. Patients will continue on their dosing regimen considered to constitute the lowest clinically efficacious dose to maintain clinical efficacy in individual patients.

The study duration of CACZ885GFR01 study will be extended until canakinumab (Ilaris®) is commercially available for all indications.

Changes to the protocol are related to the following sections:

- Section 1.1. Background
- Section 1.2. Purpose
- Section 3.1. Study design
- Section 3.3. Rationale of dose/regimen, route of administration and duration of treatment
- Section 3.5. Risks and benefits
- Section 4. Population
- Section 5. Treatment
- Section 6. Visit schedule and assessments
- Section 9.4. Analysis of variables

Amendment 2

The purpose of this study CACZ885GFR01 is to provide continuous Ilaris® (canakinumab) treatment to patients in France who completed Study CACZ885G2301E1 (long term phase III study) until this medication is commercially available and reimbursed in France for the systemic Juvenile Idiopathic Arthritis indication. The current version of the protocol stipulates that the treatment period will be a maximum 12 months or could end sooner if Ilaris® was commercially available in France.

Because it is anticipated that the reimbursement of Ilaris® (canakinumab) may not be achieved at actual date of study completion, the study duration will be extended (one year extension).

Changes to the protocol are related to the following sections:

- Section 1.1. Background
- Section 1.2. Purpose
- Section 3.1. Study design
- Section 6. Visit schedule and assessments

Amendment 1

The purpose of amendment 1 is to make clear that Novartis will supply the open-label investigational drug (canakinumab) from commercial packages or clinical batches.

Furthermore, amendment 1 also addresses the request from the investigators to add the option to reduce the canakinumab dose in patients with adequate response by prolonging the canakinumab dose interval (i.e. every 6 or 8 weeks) according to clinical response and investigators judgment.

Changes to the protocol are related to the following sections:

- Section 5.1.1 Investigational treatment
- Section 5 Treatment
- Section 6. Visit schedule and assessments

Protocol synopsis

Protocol number	CACZ885GFR01
Title	A French open-label extension study of canakinumab in patients who participated in international phase III studies CACZ885G2301E1 or CACZ885G2306 in Systemic Juvenile Idiopathic Arthritis and CACZ885N2301 in Hereditary Periodic Fever (TRAPS, HIDS or crFMF).
Brief title	French study extension to study CACZ885G2301E1, CACZ885G2306 and CACZ885N2301.
Sponsor and Clinical Phase	Novartis Pharma SAS III
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of this study is to provide continuous canakinumab (Ilaris®) treatment to patients in France who completed study CACZ885G2301E1, CACZ885G2306 or CACZ885N2301. The local extension study will be completed as soon as canakinumab is commercially available and reimbursed in France for these indications, or if applicable, when it will be confirmed that the last indication could not be reimbursed in France. However, as the commercialization of the different indications will be effective at different dates, patients will discontinue the study indication by indication. This study will only be proposed to French centers involved into study CACZ885G2301E1, CACZ885G2306 and CACZ885N2301.
Objective(s)	The objective of this extension protocol is to collect safety data (serious and non-serious adverse events) and to provide continuous canakinumab to patients in France who completed study CACZ885G2301E1, CACZ885G2306 or CACZ885N2301 until a decision regarding reimbursement in France is effective for canakinumab (Ilaris®) in these indications.

Study design	This is an open-label (single treatment arm) extension safety study for patients who completed the international studies: • CACZ885G2301E1 • or CACZ885N2301 • or CACZ885G2306 The last visit of study CACZ885G2301E1, CACZ885G2306 or CACZ885N2301 will be the first visit of this extension study. Patients follow up: For patients previously included in study CACZ885G2301E1 (SJIA indication) These patients will continue the same dosing regimen used at the end of CACZ885G2301E1. Visits will take place at canakinumab dose administrations, approximately every 4 weeks (or less frequently according to investigators judgment i.e. 6, 8 or 12 weeks). The safety of canakinumab will be evaluated (adverse events and serious adverse events collection). Patients will be followed up according to SmPC (see appendix 1) and local practice. For patients previously included in study CACZ885N2301 (Periodic Fever syndromes) These patients will continue the maintenance dose as determined at the end of the open-label period/ epoch 4 (i.e the lowest clinically efficacious dose to maintain clinical efficacy in individual patients with a good tolerability). Visits will take place at scheduled administration dates, approximately every 4, 8 or 12 weeks. The safety of canakinumab will be evaluated (adverse events and serious adverse events). Patients will then be followed up according to SmPC approved by EMA (European Medicines Agency). For patients previously included in study CACZ885G2306 (SJIA) These patients will continue on their dosing regimen considered to constitute the lowest clinically efficacious dose to maintain clinical efficacy in individual patients. Visits will take place at canakinumab dose administration, approximately every 4, 8 or 12 weeks. The safety of canakinumab will be evaluated (adverse events and serious adverse events collection). Patients will be followed up according to SmPC (see appendix 1) and investigators judgment.
Population	Up to 40 patients may be included in the French extension study CACZ885GFR01 (in 3 centers). • Twelve patients previously enrolled into study CACZ885G2301E1 • Up to 28 potential additional patients according to amendment 3: o Up to 21 patients included in CACZ885G2306 study (in 3 French centers) o Up to 7 patients included in CACZ885N2301 study (in 3 French centers).

Inclusion criteria	Criteria applicable for patients with Systemic Juvenil Idiopathic Arthritis SJIA) ▸ Patients who have completed the international studies CACZ885G2301E1 or CACZ885G2306 without any significant safety issue according to Investigator's opinion. ▸ Patients who have completed the international CACZ885G2306 study and who successfully withdrew canakinumab treatment per protocol but with a disease relapse after the end of study visit will be allowed to participate in CACZ885GFR01 study (whatever the time of relapse from the end of study visit), if the investigator states that there is an indication to resume canakinumab. ▸ Patients who have participated in the international CACZ885G2306 study but could not be randomized and then have continued canakinumab in part I until the end of the study at a dose of 4 mg/kg every 4 weeks may be switched to CACZ885GFR01 study if the investigator thinks that, in the interest of the patient, there is an indication to taper off canakinumab dose after a prolonged remission. Criteria applicable for patients with Periodic Fever syndromes (TRAPS, HIDS, crFMF) ▸ Patients who have completed the international CACZ885N2301 study without any significant safety issue according to Investigator's opinion. Criteria applicable for all patients ▸ Parent's or legal guardian's written informed consent and child's assent, if appropriate, or patient's written informed consent for patients ≥ 18 years of age must be obtained before any study related activity or assessment is performed.
Exclusion criteria	1. History of recurring infections, or underlying conditions which may predispose them to infections. Treatment with canakinumab should not be continued in patients with severe infections requiring medical intervention. 2. Hypersensitivity to the active substance or to any of the excipients (see SmPC, section 6.1). 3. Concomitant use of second line agents such as disease-modifying and/or immunosuppressive drugs will not be allowed with the exception of: • Methotrexate, and folic/folinic acid supplementation (according to standard medical practice) • Non-steroidal anti-inflammatory drug (NSAID) • Systemic corticosteroid treatment. 4. Concomitant use of another biologic agent or any investigational drug. 5. Pregnant or nursing (lactating) female patients, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test or an urinary pregnancy test. 6. Female patients who are of child-bearing potential defined as all females physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment.

Treatment	All patients will be treated with canakinumab. For patients previously included in study CACZ885G2301E1 (SJIA) These patients will continue the same dose as their last dose administered in the study CACZ885G2301E1: canakinumab 4mg/kg (or 300mg max) or 2mg/kg (150mg/max) every 4 weeks (or less frequently according to investigators judgment i.e. 6, 8 or 12 weeks). For patients previously included in study CACZ885G2301E1, the canakinumab dose interval may be prolonged (i.e. every 8 or 12 weeks) in patients with adequate response according to the clinical response and investigators judgment. For patients previously included in study CACZ885N2301 (Periodic Fever syndromes) These patients will continue on their last dosing regimen of the open-label long term treatment epochs (Epochs 4) considered to constitute the lowest clinically efficacious dose to maintain clinical efficacy in individual patients. Patients will then continue one of the following regimen: - Canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q4w - Canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q8w - Canakinumab 300 mg (or 4 mg/kg for patients weighing ≤40 kg) q4w - Canakinumab 300 mg (or 4 mg/kg for patients weighing ≤40 kg) q8w. In case of re-flare (according to investigators judgment), patients will be allowed to increase the dose as follows: - If patients receive canakinumab 150 mg q8w, the dose of canakinumab will be increased to 150 mg q4w - If patients receive canakinumab 150 mg q4w, the dose of canakinumab will be increased to 300 mg q4w - If patients receive canakinumab 300 mg q8w, the dose of canakinumab will be increased to 300 mg q4w. For patients previously included in study CACZ885N2301, the canakinumab dose interval may be prolonged (i.e. every 8 or 12 weeks) in patients with adequate response according to the clinical response and investigators judgment. For patients previously included in study CACZ885G2306 (SJIA): These patients will continue the same dose as their last dose administered at the end of the tapering period study CACZ885G2306. Then, patients will continue one of the following regimens: - Canakinumab 4mg/kg q4wks - Canakinumab 2mg/kg q4wks - Canakinumab 1mg/kg q4wks - Canakinumab 4mg/kg q8wks - Canakinumab 4mg/kg q12wks. Patients may receive an up-titration if they re-flare (maximum dose of 300 mg (or 4 mg/kg s.c for patients ≤40 kg) q4w). Patients who successfully withdrew canakinumab per protocol but with a disease relapse will be allowed to participate in CACZ885GFR01 study (whatever the time of relapse from the end of study visit) and will receive a starting dose of 4 mg/kg s.c (300 mg for patients ≥40 kg) every 4 weeks. This dose (or dose interval) may be adjusted according to the response and investigators judgment. For patients previously included in study CACZ885G2306, the canakinumab dose interval may also be prolonged (i.e. every 8 or 12 weeks) in patients with adequate response according to the clinical response and investigators judgment. For all indications, the maximum canakinumab dose is 4 mg/kg or 300 mg for patients ≥ 40 kg.

Investigational treatment	Novartis has been supplying the open-label investigational drug (canakinumab) under the form of a lyophilisate in vial. A marketing authorization has been granted in February 2017 by the European Commission for canakinumab as a solution for injection. If necessary (for logistic reasons), Novartis may supply one or the other pharmaceutical form for the trial. There will not be any change for the patient in the way the medication is administered (subcutaneously).
Efficacy assessments	There is no efficacy assessment in this study
Safety assessments	AEs and SAEs will be collected
Other assessments	None
Data analysis	The data will be presented in a descriptive manner. Adverse events will be coded using the MedDRA dictionary that provides the primary system organ class and preferred term information. Adverse events will be summarized for each indication by presenting the number and percentage of patients having any adverse event, having any adverse event in each primary system organ class and having each individual adverse event based on the preferred term. All other information collected (e.g. severity, relationship to study drug, or microorganism for infectious adverse events) will be tabulated and listed as appropriate. Deaths, serious adverse events, and adverse events leading to discontinuation of study drug will be summarized by primary system organ class and preferred term and listed. The exposure to study drug (number of injections) and duration of exposure (days) will be summarized and listed.

1 Introduction

1.1 Background

Systemic Juvenile Idiopathic Arthritis (SJIA) is a subset of Juvenile Idiopathic Arthritis (JIA), a serious and potentially disabling form of arthritis that occurs in children 16 years of age and younger, and accounts for approximately 4 - 17 % of JIA (Quartier 2007, Ravelli and Martini 2007). In contrast to other JIA subtypes SJIA is associated with systemic symptoms such as fever, rash, anemia, leukocytosis, elevated erythrocyte sedimentation rate and acute-phase. The peak age of disease onset lies between 18 months and 2 years, but SJIA may occur in children of any age and, rarely, in young adults too (Woo 2006).

Several lines of evidence show that interleukin-1 (IL-1) plays a pivotal role in the pathogenesis of SJIA (Dinarello 2005, Pascual et al 2005).

Ilaris® (Canakinumab) is a human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1/κ isotype. Canakinumab binds with high affinity specifically to human IL-1 beta and neutralizes the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators. Canakinumab has a half-life of approximately 21-28 days.

To date, four clinical studies (CACZ885A2203, CACZ885G2305, CACZ885G2301, and CACZ885G2301E1) have been performed by Novartis to evaluate canakinumab as a treatment for patients with SJIA.

Ilaris® received Marketing Authorization by the EMA for patients with Systemic Juvenile Idiopathic Arthritis (SJIA) on August 2013 for *the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Ilaris® can be given as monotherapy or in combination with methotrexate.*

Study CACZ885G2301E1 is a Phase III study designed to assess long-term safety and efficacy data for patients with SJIA who either participated in the CACZ885G2305 and CACZ885G2301 registration studies or were treatment-naive to canakinumab. In France, 48 patients were enrolled in the CACZ885G2301E1 study at four centers (Necker, Kremlin- Bicêtre, Lyon, and Strasbourg). Study CACZ885G2301E1 is ending on November 2014 and 3 sites (Necker, Kremlin-Bicêtre, and Lyon) still have patients under treatment.

Novartis Pharma France wished to set up a local protocol to allow patients who benefited from canakinumab treatment received in the CACZ885G2301E1 study to continue to receive canakinumab treatment until canakinumab (Ilaris®) is available and reimbursed on the French market for the SJIA indication.

Amendment 3 has been proposed to open the recruitment of study CACZ885GFR01 to patients who will complete:

- the phase III international study (CACZ885N2301) designed to assess efficacy and tolerability of canakinumab in patients suffering from 3 rare Hereditary Periodic Fevers (TRAPS, HIDS or crFMF),
- and the phase III international study CACZ885G2306 designed to assess 2 different canakinumab taper regimens in patients with clinical remission (inactive disease for at least 24 continuous weeks) on canakinumab treatment in SJIA.

The objective of amendment 3 is to provide continuous treatment to these patients once they have completed CACZ885N2301 or CACZ885G2306 until the medication is commercially available in France for these new indications.

- Study CACZ885N2301 in Hereditary Periodic Fevers (TRAPS, HIDS or crFMF)

CACZ885N2301 is a randomized, double-blind, placebo controlled study with subsequent randomized withdrawal/ dosing frequency reduction and open-label long term treatment epochs. In this study, an initial dose regimen of 150 mg s.c (or 2 mg/kg for patients ≤ 40kg) every 4 weeks (q4w) has been used while allowing for up-titration to a maximal dose of canakinumab 300 mg (or 4 mg/kg for patients weighing ≤40 kg) q4w to optimize the regimen and thus achieve efficacy in difficult cases.

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

The dose regimen used in the open-label long term treatment epochs (maintenance dose; Epochs 4) is considered to constitute the lowest clinically efficacious dose to maintain clinical efficacy in individual patients. A total of 181 patients (46 TRAPS, 63 HIDS, 72 crFMF) was randomized in 15 countries worldwide. The protocol included patients as young as 2 years old.

In order to support regulatory filing, the analyses of the primary efficacy variable and all secondary efficacy and safety variables up to Week 16 were performed after all patients completed the final visit of the randomized treatment epoch (Epoch 2) of the study.

Epoch 2 results from study CACZ885N2301 provide strong evidence of the superiority of canakinumab over placebo. Canakinumab has shown a fast onset of response and efficacious control of clinical signs, symptoms and serological manifestations in all 3 cohorts of crFMF, HIDS and TRAPS patients.

As shown in table 1 below, the primary objective was achieved for all indications (TRAPS, HIDS and crFMF): canakinumab was superior to placebo in the proportion of patients who resolved their index disease flare at Day 15 and had no new flare over the 16 weeks of treatment.

Canakinumab also demonstrated superior efficacy compared to placebo on the secondary endpoints of global assessment disease activity (PGA) < 2 and CRP ≤ 10 mg/L for all cohorts.

Table 1. Comparison between treatment groups for patients who responded at week 16 by cohort (ITT)

	ACZ885 150mg q4w		Placebo comparison		Treatment		
Cohort	n/M	95% CI	n/M	95% CI	Risk difference	Odds Ratio	One-sided p-
crFMF	19/31 (61.29)	(42.19, 78.15)	2/32 (6.25)	(0.77,	0.55 (0.31, 0.73)	23.75 (4.38, 227.53)	<0.0001*
HIDS	13/37 (35.14)	(20.21, 52.54)	2/35 (5.71)	(0.70,	0.29 (0.06, 0.50)	8.94 (1.72, 86.41)	0.0020*
TRAPS	10/22 (45.45)	(24.39, 67.79)	2/24 (8.33)	(1.03,	0.37 (0.08, 0.61)	9.17 (1.51, 94.61)	0.0050*

n=number of patients who responded; M=number of patients evaluated for response; CI=confidence Interval.
* indicates statistical significance (one-sided) at the 0.025 level based on Fisher exact test.

There were no new or unexpected safety findings in the canakinumab-treated patients through epoch 2. Similar to what was observed in SJIA patients treated with canakinumab, the most frequently affected SOC in crFMF, HIDS and TRAPS patients was infections and infestations, with the most common infections being those of the upper respiratory tract.

As a result of this positive interim analysis at the end of Epoch 2, a registration dossier was submitted to the EMA on April 2016. A marketing authorization has been granted in EU in March 2017.

The first French patients included CACZ885N2301 will complete the study from November 2016. According to amendment 3, patients who have beneficiated from canakinumab treatment will then been enrolled in the French CACZ885GFR01 study.

- Study CACZ885G2306 in SJIA

Study CACZ885G2306 has been requested by EMA and designed to assess 2 different canakinumab taper regimens in patients with SJIA with clinical remission on canakinumab treatment (inactive disease for at least 24 continuous weeks) without concomitant CS or MTX. Data from this study will be used to help guide physicians regarding canakinumab dose reduction in appropriate SJIA patients.

Eligible patients were entered Study Part I during which all patients were treated with canakinumab 4 mg/kg every 4 weeks until they qualify and enter Part II of the study.

Patients who become eligible for randomization enter the Study Part II and undergo canakinumab tapering (to receive canakinumab at either a reduced dose or a prolonged dose interval). Part II is a 72-week randomized treatment / follow-up period (48 weeks of canakinumab tapering followed by 24 weeks of follow-up while completely off-treatment).

Patients who do not become eligible for randomization may remain in Study Part I for the duration of the study, and since patients who fail any of the 3 canakinumab tapering steps during Part II may remain in Study Part II for the duration of the study, both study parts have been assigned an estimated maximum duration (for a given patient) of 216 weeks).

The study population consists of male and female patients aged ≥ 2 to < 20 years in two cohorts:

Cohort 1: Patients previously participating in Study CACZ885G2301E1 who at the time of evaluation for participation in CACZ885G2306 were treated with canakinumab 4mg/kg and had inactive disease

Cohort 2: Patients, who at screening had active SJIA and were canakinumab treatment-naïve.

A total of 172 patients have been enrolled (25 patients were enrolled in 3 French centers).

The objective of CACZ885GFR01 study is to collect additional safety data (serious and non- serious adverse events) and provide continuous canakinumab treatment for patients completing studies CACZ885G2301E1, CACZ885N2301 or CACZ885G2306 in France pending reimbursement of canakinumab (Ilaris®) in these indications.

1.2 Purpose

The purpose of this study is to provide continuous canakinumab treatment to patients in France who completed the following studies: CACZ885G2301E1, CACZ885N2301 or CACZ885G2306 until canakinumab (Ilaris®) is commercially available and reimbursed in France for these indications.

This local extension study will only be proposed to the 4 French centers involved into CACZ885G2301E1, CACZ885N2301 or CACZ885G2306 study.

2 Study objectives

The objective of this protocol is to collect additional safety data (serious and non-serious adverse events) and to provide continuous Ilaris® (canakinumab) treatment to patients in France who completed CACZ885G2301E1, CACZ885N2301 or CACZ885G2306 study.

3 Investigational plan

3.1 Study design

This is an open-label (single treatment arm) extension period for patients in France who have completed the international studies:

- CACZ885G2301E1
- or CACZ885N2301
- or CACZ885G2306.

The last visit of CACZ885G2301E1, CACZ885N2301 or CACZ885G2306 studies will be the first visit of this extension study.

Patients follow up:

Patients previously included in study CACZ885G2301E1 (SJIA):

These patients will continue the same dosing regimen used at the end of CACZ885G2301E1.

Visits will take place at canakinumab dose administration dates, approximately every 4 weeks (or less frequently according to investigators judgment i.e. 6, 8 or 12 weeks). The safety of canakinumab will be evaluated (adverse events and serious adverse events). Patients will be followed up according to SmPC (see appendix 1) with possible adaptation based on investigators judgment related to specific patient medical consideration.

Patients previously included in study CACZ885N2301 (Periodic Fever syndromes indications: TRAPS, HIDS or crFMF):

These patients will continue the maintenance dose as determined at the end of the open-label period/ epoch 4 (i.e the lowest clinically efficacious dose to maintain clinical efficacy in individual patients with a good tolerability).Visits will take place at scheduled administration

dates, approximately every 4, 8 or 12 weeks. The safety of canakinumab will be evaluated (adverse events and serious adverse events collection). Patients will then be followed up according to SmPC with possible adaptation based on investigators judgment related to specific patient medical consideration.

Patients previously included in study CACZ885G2306 (SJIA indication):

These patients will continue on their dosing regimen considered to constitute the lowest clinically efficacious dose to maintain clinical efficacy in individual patients.

Visits will take place at canakinumab dose administrations, approximately every 4, 8 or 12 weeks according to the individual drug regimen of the end CACZ885G2306 and investigators judgment. The safety of canakinumab will be evaluated (adverse events and serious adverse events collection). Patients will be followed up according to SmPC (see appendix 1) with possible adaptation based on investigators judgment related to specific patient medical consideration.

The study duration will depend on the date of reimbursement of canakinumab (Ilaris®) in France for the new indications and will be extended until the medication is commercially available for each indication. However, as the commercialization of the different indications may be effective at different dates, the patients will discontinue indication by indication (see section 5; end of treatment).

3.2 Rationale of study design

Given the purpose of this extension study, an open-label design is appropriate.

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

Patients with SJIA will be treated with canakinumab in an open-label manner and followed up according to the approved European SmPc (appendix 1).

For patients with Periodic Fever syndromes (TRAPS, HIDS or crFMF), the dose of used in the extension study will not exceed the maximum dose used in CACZ885N2301 (300mg/ 4 mg/kg for patients weighing ≤40 kg). The patients will then be followed up according the European SmPc once available after EMA authorization.

3.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.5 Risks and benefits

Canakinumab offers a new therapeutic option for patients with SJIA or Periodic Fever syndromes who do not respond to standard therapy. Canakinumab enables patients to control their disease and reduce their use of steroids, a main cause of impaired growth and side effects in SJIA or Periodic Fever syndromes children. All the patients included in this extension study have demonstrated clinical response to canakinumab treatment for at least 2 years in study CACZ885G2301E1, CACZ885G2306 or CAC885N2301. The risk to patients in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring and adherence to the protocol guidelines for dose administration / reduction / interval prolongation / discontinuation.

4 Population

Up to 41 patients may be included in the French extension study CACZ885GFR01 (in 3 centers).

- Twelve patients previously enrolled into study CACZ885G2301E1

- Twenty nine potential additional patients according to amendment 3:
  - up to 21 patients previously enrolled into CACZ885G2306 study (in 3 centers)
  - up to 8 patients previously enrolled into CACZ885N2301 study (in 4 French centers).

4.1 Inclusion criteria

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

Criteria applicable for patients with Systemic Juvenil Idiopathic Arthritis (SJIA)

1. Patients who have completed the international CACZ885G2301E1 or CACZ885G2306 studies without any significant safety issue according to Investigator's opinion.
2. Patients who have completed the international CACZ885G2306 study and who successfully withdrew canakinumab treatment per protocol but with a disease relapse after the end of study visit will be allowed to participate in CACZ885GFR01 study (whatever the time of relapse from the end of study visit), if the investigator states that there is an indication to resume canakinumab.
3. Patients who have participated in the international CACZ885G2306 study but could not be randomized and then have continued canakinumab in part I until the end of the study at a dose of 4 mg/kg every 4 weeks may be switched to CACZ885GFR01 study if the investigator thinks that, in the interest of the patient, there is an indication to taper off canakinumab dose after a prolonged remission

Criteria applicable for patients with Periodic Fever syndromes (TRAPS, HIDS, crFMF)

1. Patients who have completed the international CACZ885N2301 study without any significant safety issue according to Investigator's opinion.

Criteria applicable for all patients

1. Parent's or legal guardian's written informed consent and child's assent, if appropriate, or patient's written informed consent for patients ≥ 18 years of age must be obtained before any study related activity or assessment is performed.

4.2 Exclusion criteria

1. History of recurring infections, or underlying conditions which may predispose them to infections. Treatment with canakinumab should not be continued in patients with severe infections requiring medical intervention.
2. Hypersensitivity to the active substance or to any of the excipients (see SmPC, section 6.1).
3. Concomitant use of second line agents such as disease-modifying and/or immunosuppressive drugs will not be allowed with the exception of:
   - Methotrexate, and folic/folinic acid supplementation (according to standard medical practice)
   - Non-steroidal anti-inflammatory drug (NSAID)
   - Systemic corticosteroid treatment.
4. Concomitant use of another biologic agent or any investigational drug.
5. Pregnant or nursing (lactating) female patients, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test or an urinary pregnancy test.
6. Female patients who are of child-bearing potential, defined as all females physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment. Effective contraception methods include:
   - 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

- 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
- Male sterilization (at least 6 months prior to inclusion). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
- 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
- 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.

Reliable contraception should be maintained throughout the study and until 3 months after canakinumab discontinuation.

5 Treatment

Initial canakinumab dose:

For patients previously included in study CACZ885G2301E1 (SJIA)

Patients will continue the same dose as their last dose administered in the study CACZ885G2301E1: canakinumab 4mg/kg (or 300mg max) or 2mg/kg (150mg max) every 4 weeks.

Canakinumab dose reduction from 4 mg/kg to 2 mg/kg every 4 weeks in steroid-free patients with prolonged strong response was permitted in the ongoing extension study CACZ885G2301E1 at the request of the treating physician and with the agreement of Novartis.

Similarly, in this study, the canakinumab dose may be reduced from 4mg/kg (300 mg max) to 2mg/kg (150 mg max) every 4 weeks and then interrupted after a prolonged remission according to the investigators judgment.

For patients previously included in study CACZ885N2301 (Periodic Fever syndromes indications: TRAPS, HIDS or crFMF)

Patients will continue one of the following regimens as received at the end of the study:

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

In case of re-flare (according to investigators judgment), patients will be allowed to increase the dose as follow:

- If patients receive canakinumab 150 mg q8w, the dose of canakinumab will be increased to 150 mg q4w
- If patients receive canakinumab 150 mg q4w, the dose of canakinumab will be increased to 300 mg q4w
- If patients receive canakinumab 300 mg q8w, the dose of canakinumab will be increased to 300 mg q4w

For patients previously included in study CACZ885G2306 (SJIA):

The patients will continue the same dose as their last dose administered at the end of the tapering period study CACZ885G2306.

Then, patients will continue one of the following regimens:

- Canakinumab 4mg/kg q4wks
- Canakinumab 2mg/kg q4wks
- Canakinumab 1mg/kg q4wks
- Canakinumab 4mg/kg q8wks
- Canakinumab 4mg/kg q12wks

The patients who have withdrawn canakinumab per protocol may resume canakinumab after a relapse at a starting dose of 4 mg/kg (maximum 300 mg) every 4 weeks.

Dose adjustments (for all patients):

Patients may receive an up-titration or may resume canakinumab if they re-flare (maximum dose of 300 mg (or 4 mg/kg s.c for patients ≤40 kg q4w).

The canakinumab dose interval (i.e. every 6, 8 or 12 weeks) may also be prolonged in patients with adequate response according to investigators judgment.

Every patient withdrawn from CACZ885GFR01 study due to a remission will be allowed to resume canakinumab in case of relapse and will be followed up again in the study.

Canakinumab will be administered at the study center.

End of treatment

For patients treated for SJIA:

Investigators will be informed as soon as this indication is commercially available in order to organize at the next planned visit the dropout of the patients. If no visit is planned within 2 months of notification reception, the investigators will have to contact the patient in order to organize patient's study termination. Investigators will have the possibility to perform a last canakinumab administration during the last visit of the protocol.

For patients treated for TRAPS, HIDS and crFMF:

Investigators will be informed as soon as this indication is commercially available in order to organize at the next planned visit the dropout of the patients. If no visit is planned within 2 months of notification reception, the investigators will have to contact the patient in order to organize patient's study termination. Investigators will have the possibility to perform a last canakinumab administration during the last visit of the protocol.

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Novartis will supply one of the following open-label investigational drugs as commercial packages or clinical batches which are labelled according to legislation in France related to clinical trial product:

- ACZ885 150mg: Active canakinumab in individual 6 mL glass vials, each containing 150 mg canakinumab lyophilisate in vial.

Or

- ACZ885 150 mg/ 1 mL : 1mL of solution for injection in a 2 mL vial (type I glass) with a stopper (laminated chlorobutyl rubber) and flip-off cap (aluminium).

The maximal total single dose of canakinumab allowed is 300 mg, which is administered as two subcutaneous 150 mg injections once every 4 weeks.

5.1.2 Additional study treatment

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

5.2 Treatment arms

All patients will receive canakinumab as investigational drug medication.

5.3 Treatment assignment, randomization

All patients will be treated with active open-label canakinumab.

5.4 Treatment blinding

Not applicable.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number, assigned at inclusion composed by the site number assigned by Novartis and a sequential number. In this study, the patient will keep the same identifier as in study CACZ885G2301E1/CACZ885N2301/CACZ885G2306.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with investigational treatment labelled according to legislation in France related to clinical trial product.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

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

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

The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of other study treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

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

Study drug dose adjustments and/or interruptions are permitted, according to the investigator judgment. These changes must be recorded on the Dosage Administration Record CRF.

5.5.6 Rescue medication

Not applicable

5.5.7 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug.

5.5.8 Prohibited Treatment

The expression of hepatic CYP450 enzymes may be suppressed by the cytokines that stimulate chronic inflammation, such as IL-1 beta. Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as canakinumab, is introduced. This is clinically relevant for CYP450 substrates with a narrow therapeutic index where the dose is individually adjusted. In patients being treated with this type of medicinal product while on canakinumab, therapeutic monitoring of the effect or of the active substance concentration should be performed and the individual dose of the medicinal product adjusted as necessary.

Use of canakinumab with TNF inhibitors is not recommended because this may increase the risk of serious infections (an increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors)

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving canakinumab. Therefore, live vaccines should not be given concurrently with canakinumab, but prior to initiating Ilaris® therapy.

5.5.9 Discontinuation of study treatment and premature patient withdrawal

Patients may voluntarily withdraw from the study for any reason at any time. Study treatment must be discontinued under the following circumstances:

- The availability of repaid product in France for the patient's disease,
- If, on balance the investigator believes that continuation would be detrimental to the patient's well-being,
- Unsatisfactory therapeutic effect based on investigator judgment,
- Use of prohibited treatment / Protocol violation,
- Onset of malignancy,
- Occurrence of an uncontrolled life-threatening infection,
- Pregnancy,
- Other Adverse Event needing study discontinuation,
- Lost to follow-up,
- Administrative reasons,

- Death.

If premature withdrawal occurs for any reason, the investigator must make every effort to complete End of study visit in the CRF and to determine the primary reason for a patient's premature withdrawal from the study and record this information.

5.5.10 Emergency breaking of treatment assignment

Not applicable

5.5.11 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests.

6 Visit schedule and assessments

Visits will take place at the patient's scheduled drug administration date (approximately every 4 weeks or less frequently according to investigators judgment i.e. 6, 8 or 12 weeks).

If no administration is performed within the 12 weeks of previous injection, a control visit will be performed at Week 13 +/- 7 days after the last administration in order to evaluate safety and need for the patient to continue the treatment and the study.

Table : scheduled visits and evaluations

Visits	**Inclusion**[1]	**Visits for canakinumab administration**[4]	**End of the study visit** [2]
Visit window (days)	+/- 7	+/- 7	+/- 7
Inclusion/ exclusion criteria	X		
Written informed consent	X		
Demographic data	X		
Treatment administration	X	X	X
Concomitant treatment	X[3]	X	X
Adverse events		X	X
End of the study			X

1) The date of last visit of CACZ885G2301E1/CACZ885N2301/CACZ885G2306 study will be the first visit of this extension study.

2) The end of study is defined as premature termination or end of the study according to protocol: in the month following the availability of repaid product in France.

3) Corticosteroids and methotrexate only.

4) Visits will take place at scheduled administration date every 4, 6, 8 or 12 weeks (section 5). Dose interval may be prolonged during the study (i.e. visits every 6, 8 or 12 weeks or longer in case of adequate response at the discretion of the investigator (section 5). If no administration is performed within the 12 weeks of previous injection, a control visit will be performed at Week 13 +/- 7 days after the last administration in order to evaluate safety and need for the patient to continue the treatment and the study.

6.1 Patient demographics/other baseline characteristics

Demography information and other baseline characteristics are those collected in CACZ885G2301E1 / CACZ885N2301 / CACZ885G2306 study.

6.2 Study treatment dispensation

Basic study treatment dispensation data will be collected (date of injection and total volume injected).

6.3 Efficacy

No efficacy data are collected in this study.

6.4 Safety

Safety assessments will consist of recording and monitoring of Adverse Events (AE) and Serious Adverse Events (SAE).

7 Safety monitoring

7.1 Adverse events

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

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

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

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

Adverse events should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study medication
- study treatment (no/yes), or
- investigational treatment (no/yes), or
- the other study treatment (non-investigational) (no/yes), or
- both or indistinguishable,
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported

- whether it constitutes a serious adverse event (SAE - See section 7.2 for definition) action taken regarding canakinumab treatment.

All adverse events should be treated appropriately. Treatment may include one or more of the following:

- no action taken (i.e. further observation only)
- study treatment dosage adjusted/temporarily interrupted
- study treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, 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 SmPC or will be communicated between SmPC updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

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

7.2 Serious adverse event (SAE)

7.2.1 Definition of a SAE

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
- 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, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Step4/E2D_Guideline.pdf).

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

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

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see ICH-E2D Guideline available at:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Step4/E2D_Guideline.pdf).

7.2.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days [after the last study visit/ following the last administration of study treatment if there are post-treatment follow-up visits with no required procedures] must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

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

Information about all SAEs (*either initial or follow up information)* is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to *the study treatment* complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE

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

If the SAE is not previously documented in the SmPC (see appendix 1) (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 investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements.

7.3 Pregnancy reporting

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

Pregnancy should be recorded on a Clinical Trial 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 pregnancy must be reported on the SAE Report 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.

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 must enter the information required by the protocol onto the Novartis CRFs that are printed on *3* -part, non-carbon-required paper. Field monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The CRFs pages will be collected by field monitors after monitoring validation, with one copy being retained at the investigational site. Once the CRFs pages collected, the original copy will be placed in the study Trial Master file, and the non- carbon-required copy will be forwarded to the CRO in charge of Data Management for processing.

8.3 Database management and quality control

Data from the CRFs will be entered into the study database by CRO staff, using double data entry and following their own internal standard operating procedures (that have been reviewed and approved by Novartis).

Subsequently, the entered data will be systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Other errors or omissions will be entered on Data Query Forms, which will be returned to the investigational site for resolution. The signed original and resolved Data Query Forms will be kept with the CRFs at the investigator site, and a copy will be sent to the CRO so the resolutions can be entered into the

database. Quality control audits of all key data in the database will be made prior to locking the database.

Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

After these actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

9.1 Analysis sets

Safety Set: Consists of all patients who received at least one dose of study drug and had at least one post-treatment safety assessment in the study. The statement that a patient had no adverse event (AE) also constitutes a safety assessment.

9.2 Patient demographics and other baseline characteristics

Demographics, background data and key baseline characteristics are those collected in the CACZ885G2301E1 study. Sex and date of birth will be re-collected in the CRF.

9.3 Treatments

The exposure to study drug (number of injections) and duration of exposure (days) will be summarized and listed by dose.

9.4 Analysis of variables

9.4.1 Variables

a. Efficacy variables

There is no efficacy assessment in this study

b. Safety variables

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

- Adverse events (including infections)
- Infectious adverse events

Adverse events will be summarized for each disease by presenting the number and percentage of patients having any adverse event, having any adverse event in each primary system organ class and having each individual adverse event based on the preferred term. All other information collected (e.g. severity, relationship to study drug, or microorganism for infectious adverse events) will be tabulated and listed as appropriate.

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

9.4.2 Statistical model, hypothesis, and method of analysis

This is an open-label single-arm safety trial for patients and the data will be presented in a descriptive manner.

9.4.3 Handling of missing values/censoring/discontinuations

Missing values will not be handled but premature discontinuation will be fully described.

9.5 Interim analyses

Not required

9.6 Sample size calculation

No sample size calculation was performed for this extension study which will include all eligible subjects who complete CACZ885G2301E1 or CACZ885N2301 study and meet the eligibility criteria.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 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 of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

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

Women of child bearing potential should 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 should not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. 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 Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

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

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as requests to approve deviations will not be granted.

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

If the 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 it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. 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, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days or less, if required by local regulations.

12 References

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13 Appendix 1: Summary of product characteristics