

Global Clinical Development - General Medicine

ACZ885/ Canakinumab

*CACZ885NTR01 / NCT02756650*

An open label, exploratory study to establish the efficacy and safety of 1 year Canakinumab treatment in Behçet's Disease Patients with Neurologic or Vascular Involvement

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## List of abbreviations

AE	Adverse event
BDCAF	Behçet's Disease Current Activity Form
SAE	Serious adverse event
CRF	Case Report/Record Form (paper or electronic)
CNS	Central Nervous System
CPO	Country Pharma Organization
CRO	Contract Research Organization
CSF	Cerebrospinal Fluid
EDSS	Expanded Disability Status Scale
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
i.v.	intravenous
IRB	Institutional Review Board
NBDS	Neuro-Behçet's disease
Modified EDSS	Modified Expanded Disability Status Scale
VAS	Visual Analog Scale
IV MP	Intravenous Methyl Prednisolone
PK/PD	Pharmacokinetics/ Pharmacodynamic

## SAE Serious adverse event Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical Epochs are: screening/recruitment, wash-out, treatment, and follow-up
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 <i>includes</i> 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 <i>does not include</i> protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Period	A subdivision of a cross-over study
Premature subject/patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
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

## Protocol summary

Protocol number	CACZ885NTR01
Title	<i>An open label, exploratory study to establish the efficacy and safety of 1 year Canakinumab treatment in Behçet's Disease Patients with Neurologic or Vascular Involvement</i>
Brief title	<i>Efficacy and Safety of Canakinumab in Behçet's Disease Patients with Neurologic or Vascular Involvement</i>
Sponsor and Clinical Phase	<i>Novartis Phase 2 Exploratory Study</i>
Investigation type	<i>Drug</i>
Study type	<i>An open label Phase 2 Study</i>
Purpose and rationale	<i>Study objective is to evaluate efficacy and safety of canakinumab in neurologic and vascular subtypes of Behçet's disease (BD).</i>
Primary Objective(s)	<i>Primary objective of the study is to evaluate the safety and efficacy of canakinumab on the clinical and inflammatory findings of BD patients with neurologic and vascular involvement.</i>
Secondary Objectives	<i>Secondary objectives include analyses measuring the effects of canakinumab on radiological findings (neurologic and vascular), cerebrospinal fluid (CSF) findings (neurologic), and [REDACTED] [REDACTED] aiming to investigate the biology of inflammatory attacks and their response to IL-1 blockade in parallel with clinical findings.</i>
Study design	<i>The study will be conducted as an exploratory open-label pilot trial. There will be only one treatment arm. The improvement will be evaluated in comparison to the findings recorded at the baseline.</i>
Population	<i>Biologic naïve patients aged over 18 with BD fulfilling the International Study Group (ISG) criteria, who have a recent exacerbation of large-vessel vascular disease and/or parenchymal neurologic disease (within the last month).</i>
Inclusion criteria	<p><b>For NBS :1)</b> Patients experiencing an acute exacerbation of parenchymal neurologic disease involving brainstem and/or diencephalic region with in last month.</p> <p>Exacerbation is defined based on the presence of both of the following:</p> <ol style="list-style-type: none"> <li>a. An acute/subacute neurological syndrome including any of hemiparesis, ataxia, dysarthria within the first month</li> </ol>

	<p>of onset of neurologic manifestations (without any prior high dose steroid treatment)</p> <p>b. Compatible cranial MRI lesion involving brainstem and/or diencephalic region</p> <p>2) Patients aged over 18-60 BD fulfilling the International Study Group (ISG) criteria, who have exacerbation of large-vessel vascular disease and/or parenchymal neurologic disease <i>with in last month.</i></p> <p><b>For Vascular Disease :</b></p> <p>1)Patients experiencing an acute exacerbation of vascular disease within the last month, involving</p> <p>a. Large arteries (abdominal aorta, pulmonary arteries, extremity arteries)</p> <p>b. Large veins (deep vein thrombosis of extremities, caval vein thrombosis, dural sinus thrombosis)</p> <p>c. Compatible radiological findings (spiral CT, MR, or Doppler ultrasonography)</p> <p>2) Patients aged over 18-60 BD fulfilling the International Study Group (ISG) criteria, who have exacerbation of large-vessel vascular disease and/or parenchymal neurologic disease <i>with in last month.</i></p>
Exclusion criteria	<p><b>For NBS:</b></p> <ol style="list-style-type: none"><li>1. Presence of severe neurological sequelae from any previous attacks rendering the patient dependent on others physically or mentally</li><li>2. Any other neurological cause underlying the picture including ischemic CNS lesion on MRI</li><li>3. Any previous treatment with biological agents other than interferon-alpha or any previous treatment with cyclophosphamide</li></ol>

**For Vascular disease**

4-Presence of severe vascular sequelae from any previous attacks rendering the patient dependent on others

5-Any other vascular disease complication the evaluation of exacerbation

6-Any previous treatment with biological agents other than interferon-alpha, or any previous treatment with cyclophosphamide

**General**

7- Presence or history of any other inflammatory rheumatic disease

8- Use of the listed treatment

- a. interferon-alpha in the last 6 months,
- b. IVMP in the past month

9- Positive PPD test (according to local guidance) where an active TB infection cannot be excluded via Quantiferon (T-Spot or radiographic imaging if needed) If PPD test or Quantiferon-Gold assay result shows latent TB infection without signs of active tuberculosis disease, patient will be allowed to enter in the study, when the patient agrees to start taking isoniazid prophylaxis along with the study drug for 9 months.

10- Pregnancy or lactation

11-Presence of any active or chronic infection or any major episode of infection requiring hospitalization or treatment with i.v. antibiotics within 30 days or oral antibiotics within 14 days prior to screening

12-History of a malignancy within the last 5 years, except for successfully excised squamous or basal cell carcinoma of the skin

13-Women of childbearing potential not using the contraception method(s) specified in this study, as well as women who are breastfeeding

14-With known sensitivity to canakinumab

15- Use of any other investigational agent in the last 30 days

Investigational and reference therapy	<i>Canakinumab</i>
Efficacy assessments	<i>Resolution of attacks Prevention of recurrent attacks Need for steroid usage Control of the symptoms</i>
Safety assessments	<i>All AEs and SAEs will be recorded appropriately.</i>
Other assessments	<i>PK/PD data will be collected. Canakinumab [REDACTED] will be measured in CSF.</i>
Data analysis	<i>All improvements in the [REDACTED] outcomes will be compared to the baseline, and statistical analyses will be conducted when possible.</i>
Key words	<i>Behcet's disease, Neuro-Behcet Syndrome, Disease Exacerbation, IL-1 Blockade, Canakinumab, CNS inflammation, Vasculitis</i>

## 1 Introduction

### 1.1 Background

BD is a multisystem inflammatory disorder characterised by relapsing/remitting manifestations with variable vessel vasculitis as the underlying pathology. Prevalence of BD is in a wide range between 1-420 / 100,000 depending on geographic region in the world.

Some courses of the disease carry a higher unmet need:

a. Neurologic involvement: The patients experiencing parenchymal neurologic inflammatory attacks mainly affecting the brainstem have serious morbidity and increased mortality. There is no established treatment or a clinical trial conducted to evaluate the efficacy of any drug in Neuro-Behçet disease (NBD).

b. Vascular disease: Depending on the involved large vessels (arteries and/or veins), vascular involvement has also been associated with increased morbidity and mortality. Similar to NBD there is no established treatment or a clinical trial conducted to evaluate the efficacy of any drug in large vessel vasculitis.

In recent years, some case reports showed the efficacy of canakinumab in different BD manifestations. (1,2,3,4)

Vitale et al. reported that the prompt and sustained clinical efficacy of canakinumab as a monotherapy in patients with BD supports the opportunity of using this specific anti-IL-1 $\beta$  agent as a valid therapeutic option for those cases showing a disease course resistant or refractory to multiple treatments. (1)

Cantarini et al. reported the results of canakinumab treatment in a refractory patient with BD, which was well-tolerated, and at the 6-month follow-up, no adverse events were noted. (2)

### 1.2 Purpose

Study objective is to evaluate the efficacy and safety of canakinumab in neurologic and vascular subtypes of BD.

## 2 Study objectives

**Primary objective:** Primary objective of the study is to evaluate the safety and efficacy of canakinumab on the clinical and inflammatory findings of BD patients with neurologic and vascular involvement.

**Secondary objectives:** Secondary objectives include analyses measuring the effects of canakinumab on radiological findings (neurologic and vascular), cerebrospinal fluid findings (neurologic), and [REDACTED] aiming to investigate the biology of inflammatory attacks and their response to IL-1 blockade in parallel with clinical findings.

## 2.1 Primary objective(s)

**Primary endpoint:** Resolution of acute exacerbation findings related to BD based on achievements in any of the following items without deterioration on day 30:

**For patients with parenchymal neurologic disease:** Resolution of acute exacerbation of parenchymal neurologic findings based on improvements in any of the following items without deterioration on Day 30:

- a. Improvement of muscle strength, ataxia, or other relevant neurologic findings depending on the involved region on neurological examination (by NBDS, Modified EDSS, and modified Rankin scores)
- b. Improvement in systemic inflammatory findings (CRP, ESR, SAA)
- c. Any decrease in the size of the MRI lesion, or disappearance of contrast enhancement
- d. Improvement in patients' and physicians global assessment using a 10-cm visual analogue scale (VAS)

**Complete response** will be defined as full clinical recovery to the pre-attack state, disappearance of MRI lesion(s), and normalisation of CSF findings.

**Partial response** will be defined as partial improvement in clinical findings, but with findings still worse than the pre-attack state, and MRI lesions, which become smaller with no or less enhancement, and a decrease in CSF cell count.

**Non-response** will be defined as no improvement in clinical findings, no change on MRI, no change in CSF parameters, or worsening in those findings.

**For patients with large vessel vascular disease:** Resolution of acute vascular exacerbation findings related to BD based on achievements in any of the following items without deterioration at 1 month:

- a. Improvement in relevant symptoms (localised pain, abdominal pain, calf thickness, haemoptysis) by using physician and patient's global assessment with VAS
- b. Improvement in systemic inflammatory findings (CRP, ESR, SAA)
- c. Any improvement in radiological findings depending on the involved vessels (MR, CT or Doppler findings)
- d. Improvement in patients' and physicians global assessment using a 10-cm visual analogue scale (VAS)

**Complete response** will be defined as clinical and laboratory improvement based on  $\geq 50\%$  improvements in patient's and physician's global assessments by using VAS, and  $\geq 50\%$  reduction in CRP values; along with stable or  $\geq 20\%$  reduced aneurym size in patients with arterial involvement, and stable or  $\geq 20\%$  reduced calf swelling in patients with lower extremity venous thrombosis.

**Partial response** will be defined as clinical and laboratory improvement based on observations of an improvement between 20-49% according to patient's and physician's global assessments by using VAS, 20-49% reduction in CRP values; along with stable or less than 20% reduced aneurym size in patients with arterial involvement, and stable or less than 20% reduced calf swelling in patients with lower extremity thrombosis.

**Non-response** will be defined as observing no or less than 20% clinical improvement by patient's and physician's global VAS or worsening of clinical findings, no change or increase in acute phase response, increase in aneurysm size for patients with arterial involvement or progression of venous thrombosis in patients with venous involvement.

## 2.2 Secondary objectives

### Secondary endpoints:

#### General :

Overall disease activity measures (BDCAF-Behçet's Disease Current Activity Form)

Reduced need for corticosteroid treatment (reduction of corticosteroid dosage)

Course of other BD-related manifestations

#### For NBS:

Time to at least 50% resolution of the MRI lesion as defined above

Assessment of parenchymal lesions by MR spectroscopy, and when possible with functional MRI (f-MRI) and MR-tractography

Preservation of remission within first 12 months

Number of exacerbations within 12 months

#### For vascular disease:

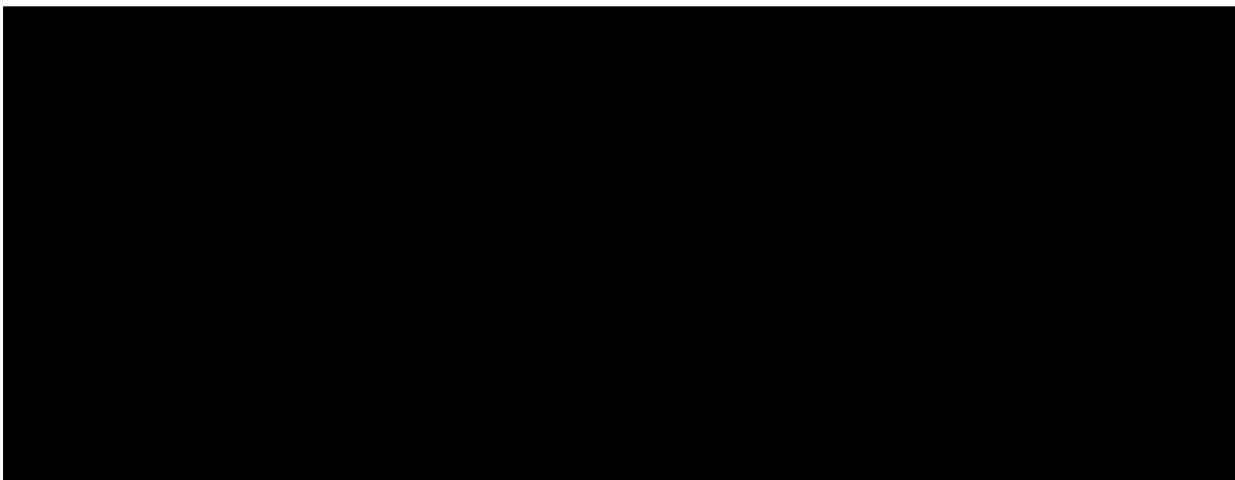
Radiological changes by PET-CT and/or MR imaging

Time to resolution as defined above

Preservation of remission within 12 months

Number of recurrent exacerbations within 12 months

PK, PD evaluations in serum and CSF

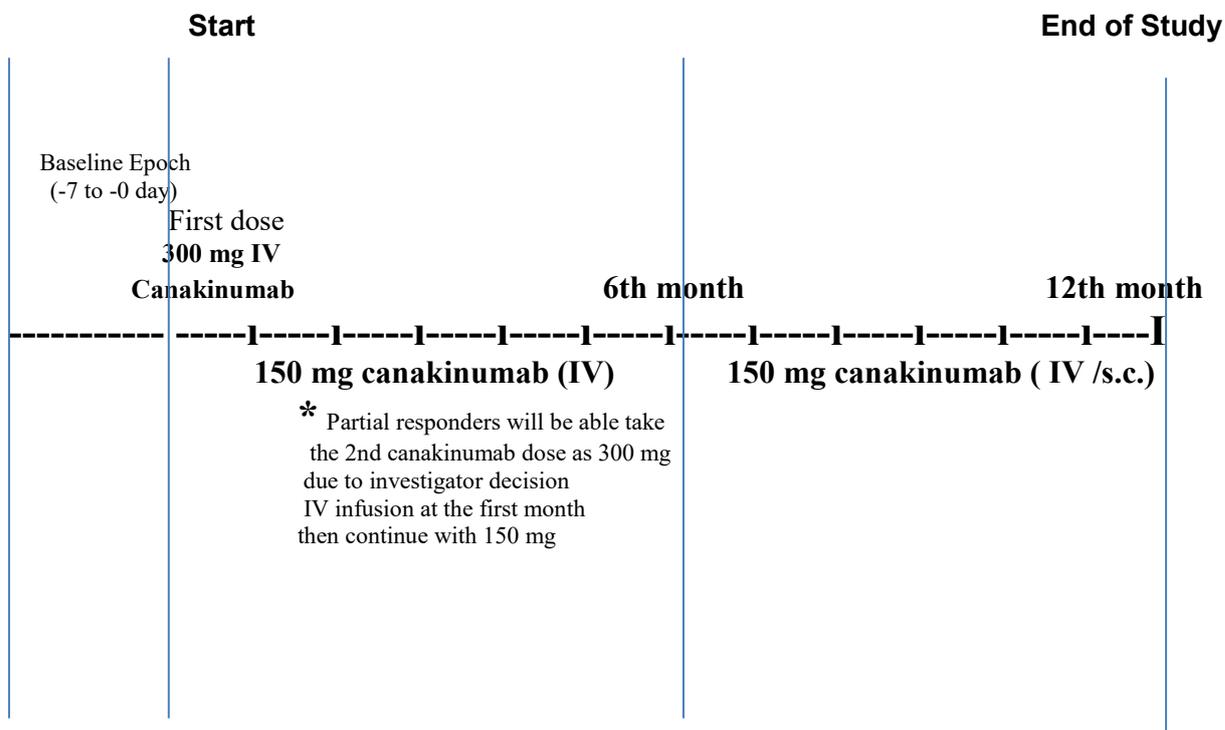


### 3 Investigational plan

#### 3.1 Study design

The study will be conducted as an exploratory open-label pilot trial. There will be only one treatment arm. The improvement will be evaluated in comparison to the findings recorded at the baseline.

Figure 3-1 Study design



Approximately 10 subjects aged 18 to 60 years, who sign an informed consent and meet all inclusion and exclusion criteria in the screening period will enter into the study. The first dose of canakinumab will be administered as 300 mg IV.

At the end of the first month, an analysis will be conducted to assess the complete, partial, and non-responders to canakinumab treatment by physician.

Partial responders will be able to take the 2nd canakinumab dose as 300 mg IV infusion at the first month then will continue the canakinumab treatment with 150 mg IV infusions at monthly intervals for 4 times. The complete responders will continue the canakinumab treatment with 150 mg IV infusions at monthly intervals for 5 times. Non-responder or deteriorating patients will be dropped from the study at the first month evaluations.

At month 6, the patients will be able to switch to SC injections or continue as IV infusions of 150 mg canakinumab for additional 6 monthly administrations. Non-responder or deteriorating patients will be dropped from the study at the first month evaluations.

### **3.2 Rationale of dose/regimen, route of administration and duration of treatment**

Canakinumab will be administered IV 300 mg initially. After the initial dose, complete responders will be given 150 mg IV infusions for every 4 weeks until month 6. A second canakinumab 300 mg IV dose will be used for patients with a partial response, and they will continue to receive 150 mg IV infusions for every 4 weeks until month 6.

Depending on the response in the first 6-month period, 150 mg canakinumab will be given as SC injections or IV infusions for every 4 weeks during the second 6-month period.

### **3.3 Rationale for choice of comparator**

There will be no active comparator.

### **3.4 Purpose and timing of interim analyses/design adaptations**

At the end of 1st month primary end point will be assessed by the physician. Complete / Partial / Non responders will be determined.

At 3rd and 6th months, there will be additional analyses to evaluate steroid tapering, prevention of disease exacerbation, and general disease activity by physician.

### **3.5 Risks and benefits**

The risk to subjects in this trial will be minimized by compliance with the inclusion/exclusion criteria, close clinical, laboratory and radiological monitoring, and application of good clinical practice principles.

## 4 Population

**Key inclusion criteria :** Biologic-naïve patients aged 18-60 years with BD fulfilling the ISG criteria, who have a recent exacerbation of large-vessel vascular disease and/or parenchymal neurologic disease.

### 4.1 Inclusion criteria

**Key inclusion criteria :** Biologic-naïve patients with BD fulfilling the ISG criteria, who have a recent exacerbation of large-vessel vascular disease and/or parenchymal neurologic disease within the last month.

**For NBS :1)** Patients experiencing an acute exacerbation of parenchymal neurologic disease involving brainstem and/or diencephalic region with in last month.

Exacerbation is defined based on the presence of both of the following:

- a. An acute/subacute neurological syndrome including any of hemiparesis, ataxia, dysarthria within the first month of onset of neurologic manifestations (without any prior high dose steroid treatment)
- b. Compatible cranial MRI lesion involving brainstem and/or diencephalic region

**2)** Patients aged over 18-60 BD fulfilling the International Study Group (ISG) criteria, who have exacerbation of large-vessel vascular disease and/or parenchymal neurologic disease *with in last month*.

#### **For Vascular Disease :**

1)Patients experiencing an acute exacerbation of vascular disease within the last month, involving

- d. Large arteries (abdominal aorta, pulmonary arteries, extremity arteries)
- e. Large veins (deep vein thrombosis of extremities, caval vein thrombosis, dural sinus thrombosis)
- f. Compatible radiological findings (spiral CT, MR, or Doppler ultrasonography)

**2)** Patients aged over 18-60 BD fulfilling the International Study Group (ISG) criteria, who have exacerbation of large-vessel vascular disease and/or parenchymal neurologic disease *with in last month*.

### 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.

#### **Key exclusion criteria**

##### **For NBS:**

1-Presence of severe neurological sequelae from any previous attacks rendering the patient dependent on others physically or mentally

2-Any other neurological cause underlying the picture including ischemic CNS lesion on MRI

3-Any previous treatment with biological agents other than interferon-alpha or any previous treatment with cyclophosphamide

#### **For Vascular disease**

4-Presence of severe vascular sequelae from any previous attacks rendering the patient dependent on others

5-Any other vascular disease complication the evaluation of exacerbation

6-Any previous treatment with biological agents other than interferon-alpha, or any previous treatment with cyclophosphamide

#### ***General***

7- Presence or history of any other inflammatory rheumatic disease

8- Use of the listed treatment

- c. interferon-alpha in the last 6 months,
- d. IVMP in the past month

9- Positive PPD test (according to local guidance) where an active TB infection cannot be excluded via Quantiferon (T-Spot or radiographic imaging if needed) If PPD test or Quantiferon-Gold assay result shows latent TB infection without signs of active tuberculosis disease, patient will be allowed to enter in the study, when the patient agrees to start taking isoniazid prophylaxis along with the study drug for 9 months.

10- Pregnancy or lactation

11-Presence of any active or chronic infection or any major episode of infection requiring hospitalization or treatment with i.v. antibiotics within 30 days or oral antibiotics within 14 days prior to screening

12-History of a malignancy within the last 5 years, except for successfully excised squamous or basal cell carcinoma of the skin

13-Women of childbearing potential not using the contraception method(s) specified in this study, as well as women who are breastfeeding

14-With known sensitivity to canakinumab

15- Use of any other investigational agent in the last 30 days

## 5 Treatment

Treatment Arm	# of Patients Entered Treatment	Type of Study Drug	Compound	Min Dose	Max Dose	Frequency	Admin. Route	Generic Acceptable?
Canakinumab	10	Investigational	ACZ	150 mg	300 mg	Monthly	IV (SC after month 6)	-

### 5.1 Protocol requested treatment

#### 5.1.1 Investigational treatment

**Canakinumab 150 mg powder for solution for infusion/injection** contains nominally 150 mg canakinumab. The vials contain an overfill of 20% i.e. resulting in a total amount of 180 mg canakinumab per vial. The overfill will allow for complete withdrawal of the labeled amount of canakinumab.

Canakinumab will be used as 300 mg IV infusions for subjects over 18 years and diagnosed as Behcet disease. The dose will be down-titrated to 150 mg IV after first dose. And there will be a switch to 150 mg SC injections after 6 months (if investigators confirm)

#### 5.1.2 Additional study treatment

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

### 5.2 Treatment arms

This is a open-label, single-arm active treatment study design.

### 5.3 Treatment assignment, randomization

At Screening (Day -7 to -0) an eligible patient will be given the lowest available number. The investigator will enter the patient number on the CRF.

### 5.4 Treatment blinding

This will be an open-label, single arm study.

## **5.5 Treating the patient**

### **5.5.1 Patient numbering**

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused.

If an enrolled patient fails to be treated for any reason, the reason will be entered on the Screening Study Disposition CRF.

### **5.5.2 Dispensing the investigational treatment**

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

### **5.5.3 Handling of study treatment**

#### **5.5.3.1 Handling of investigational treatment**

Study drug will be supplied to the study site by Novartis as open labelled bulk medication.

Study drugs 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 designated study person has access. Upon receipt, all study drugs should be stored according to the instructions specified on the drug 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 of country. They will include storage conditions for the drug, but no information about the patient except for the patient number.

The investigator or authorized site staff must maintain an accurate record of the shipment and dispensing of study drug 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 used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability log to the 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 patients will receive study medication every four weeks. Patients will receive IV infusions of canakinumab in open label study treatment period. Please refer to for study schema description.

All study treatments assigned to the patient during the study will be recorded.

Each reconstituted vial provides 150 mg of canakinumab per 1 mL.

From a microbiological point of view, once the canakinumab solution for infusion has been compounded in the infusion bag or the solution for injection has been prepared, it should be used immediately. If not used immediately, it should be administered within 24 hours (end of infusion included). If the infusion solution/solution for injection is not used within 60 minutes of preparation, it should be kept at 2-8 °C. The bags and the solution for injection should be allowed to come to room temperature for 5-10 minutes but not more than 15 minutes before administration.

Detailed instructions on the preparation and administration of the study drug will be described in the Pharmacist Manual and provided to the site.

Patients should remain at the study site for observation for 1 hour following study drug administration.

### **5.5.5 Permitted dose adjustments and interruptions of study treatment**

The first dose will be started as 300 mg IV.. At the end of the first month, an analysis will be conducted to assess the complete, partial, and non-responders to canakinumab treatment by physician.

Partial responders will be able take the 2nd canakinumab dose as 300 mg IV infusion at the first month then will continue the canakinumab treatment with 150 mg IV infusions at monthly intervals for 4 times. The complete responders will continue the canakinumab treatment with 150 mg IV infusions at monthly intervals for 5 times. Non-responder or deteriorating patients will be dropped from the study at the first month evaluations.

At the end of the 6<sup>th</sup> month the administration route can be switched to subcutaneous injection.

### **5.5.6 Rescue medication**

A rescue treatment with increased doses of prednisolone or intravenous methyl prednisolone pulses could be used depending on worsening of BD manifestations at the discretion of the investigator.

If no response or worsening of neurologic/vascular manifestations were observed in the first week, rescue treatment decision should be given with the repeated CSF and MRI (neurologic) or CT/Doppler (vascular) analyses.

Following protocol will be used as rescue treatment in patients with worsening symptoms:

For patients with neurologic involvement: 5-10 days of 1000 mg intravenous methyl prednisolone, followed by 1 mg/kg/day prednisolone, if still an insufficient response is observed, 1000 mg intravenous cyclophosphamide

For patients with vascular involvement: 3 days of 1000 mg intravenous methyl prednisolone, followed by 1 mg/kg/day prednisolone, if still an insufficient response is observed, 1000 mg iv cyclophosphamide.

### **5.5.7 Concomitant treatment**

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

### **5.5.8 Prohibited Treatment**

The following treatments are NOT allowed prior to baseline (time intervals prior to baseline are detailed below) AND during the entire study:

- Etanercept in the 4 weeks prior to the baseline visit (Day 0) and thereafter
- Riloncept in the 3 weeks prior to the baseline visit (Day 0) and thereafter
- Adalimumab in the 8 weeks prior to the baseline visit (Day 0) and thereafter
- Infliximab in the 12 weeks prior to the baseline visit (Day 0) and thereafter
- Rituximab in the 26 weeks prior to the baseline visit (Day 0) and thereafter
- Any other investigational biologics in the 8 weeks prior to the baseline visit (Day 0) and thereafter (with the exception of anakinra therapy –see below)
- Kineret (anakinra therapy) 3 days prior to the baseline visit (Day 0) and thereafter
- Leflunomide in the 4 weeks prior to the baseline visit (Day 0) and thereafter. After the completion of leflunomide treatment a cholestiramine in dose 8 g 3 times per day for 14 days is recommended.
- Thalidomide in the 2 weeks prior to the baseline visit (Day 0) and thereafter
- Cyclosporine in the 2 weeks prior to the baseline visit (Day 0) and thereafter
- i.v. immunoglobulin (i.v. Ig) in the 8 weeks prior to the baseline visit (Day 0) and thereafter
- 6-Mercaptopurine, cyclophosphamide, or chlorambucil in the 12 weeks prior to the baseline visit (Day 0) and thereafter
- Dapsone, in the 3 weeks prior to the baseline visit (Day 0) and thereafter
- Corticosteroids  $\geq 20\text{mg/day}$  or  $>0.4 \text{ mg/kg}$ , whichever applies, in the 1 week prior to the baseline visit (Day 0) and thereafter
- Live vaccinations within 3 months prior to the start of the trial, during the trial, and up to 3 months following the last dose.
- Use of other investigational non-biological drugs at the time of enrollment, within 30 days or 5 half-lives of enrolment, whichever is longer.
  - Intravenous methyl prednisolone pulse treatment within the last month

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. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug.

### **5.5.9 Discontinuation of study treatment**

Study drug must be discontinued for a given patient if the investigator determines that continuing it would result in a significant safety risk for that patient. The following circumstances require study drug discontinuation:

- Emergence of the following adverse events:
  - in the case of any severe or serious adverse event that is not compatible with administration of study medication, including adverse events that require treatment with an unacceptable co-medication,
  - in the case of onset of malignancy,
  - in the case of an uncontrolled life-threatening infection.
- Pregnancy
- Use of the prohibited concomitant medications
- Withdrawal of informed consent

#### **5.5.10 Withdrawal of consent**

Subjects also should be withdrawn at any time if the investigator concludes that it would be in the patient's best interest for any reason. Protocol deviations should not lead to patient withdrawal unless they indicate a significant risk to the patient's safety.

Subjects may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason.

If premature withdrawal occurs for any reason, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion CRF. For subjects who are lost to follow-up (i.e., those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should

show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

Every patient has the right to discontinue study participation at any time, and every patient may be discontinued from the study for any reason beneficial to his/her wellbeing. All data generated up to the time of discontinuation from the study will be analysed and the reason(s) for discontinuation will be recorded.

#### **5.5.11 Loss to follow-up**

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

#### **5.5.12 Emergency breaking of assigned treatment code**

Not applicable

#### **5.5.13 Study completion and post-study treatment**

Information on the date the subject last took drug, the subject's completion or discontinuation of the study and the reason for discontinuation of the study will be recorded on the Study Completion CRF page.



Visit	Screening ***	1***	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Day	-7 to 0	0	7	14	30	60	90	120	150	180	210	240	270	300	330	360
Blood biochemistry		X		X	X			X	X	X	X	X				
Inflammatory markers	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK markers		X	X		X	X	X			X		X				X
PD samples		X	X		X	X	X			X		X				X
MR-Doppler Imaging (PET-CT when necessary)		X	X	X	X	X	X			X		X				X
(*)CSF Puncture	X			X	X		X									
Neurological evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BDCA (BD Current Activity)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VAS for symptoms	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessment					X		X			X						X
Attack Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Steroid usage assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician&Patient Global Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug Administration		X			X	X	X	X	X	X	X	X	X	X	X	X

\*Optional

\*\* PPD test could be used within 6 months before patient study entry

**\*\*\* If needed, in Patient's emergency situation, Screening and Visit 1 assessment could be combining by the physician decisions. There is no need to be repeated same test for each visit (screening and visit 1)**

## 5.6 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.

For all patients who have signed informed consent and are entered into the next epoch of the study will have all adverse events **occurring after informed consent is signed** recorded on the Adverse Event CRF.

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.

## 5.7 Patient demographics/other baseline characteristics

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

Subjects should be seen for all post-baseline visits on the designated day with the allowance of a  $\pm 7$  day window for all visits. Subjects who discontinue study drug before completing the study, and those who prematurely withdraw from the study for any reason, should be scheduled for a visit 8 weeks ( $\pm 1$  week) after their last infusion /injection, at which time all of the assessments listed for the final visit will be performed.

Subjects who discontinue study drug also should return for a last assessment. If they refuse to return for this or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the reason for discontinuation. At a minimum, they will be contacted for safety evaluations during the 30 days following the last dose of study drug, including final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the patient record.

Information that will be collected on subjects who are screened but not enrolled includes patient demographics (age, gender, and ethnicity) and primary reason for not continuing.

If a patient discontinues before entering Visit 1, only the demographic information and Screening Log entry with the primary reason for discontinuation should be completed on the CRF. It is not necessary to complete all the required evaluations at the time of discontinuation unless medically indicated.

At screening visit information on age, sex, will be collected. Relevant medical history/current medical conditions, family medical history, will be recorded on the respective CRF page. The following should be recorded on the respective CRF page.

### 5.7.1 Laboratory tests

The investigator will evaluate the clinical significance of each laboratory value outside of the reference range. This decision should be based upon the nature and degree of the observed abnormality. The investigator may choose to repeat any abnormal result ONCE, in order to rule out laboratory error. "NCS" will be entered on the original laboratory sheet to the right of

all laboratory values, which are outside the reference range, but are judged "not clinically significant." The physician making these assessments should date and initial each form. A copy of each laboratory report must be placed in the patient's file. Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis. Repeated evaluations are mandatory until normalization or until the change is no longer clinically relevant. In case of doubt, Novartis must be contacted.

All laboratory tests will be performed in the study site except PK/PD, [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

### **5.7.2 Inflammation markers**

The following markers of inflammation, Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP) and serum amyloid A (SAA), will be performed at all scheduled visits.

### **5.7.3 Hepatitis screen, HIV screen**

In order to exclude an active hepatitis B or C or HIV infection, all subjects will undergo appropriate testing at the screening visit and. All subjects will be screened for Hepatitis B surface antigen (HBsAg). Screening for Hepatitis C will be based on HCV antibodies. A copy of the lab report must be placed in the patient's file. Evaluation for HIV seropositivity will consist of ELISA and, if positive, confirmation by Western blot will be required. Appropriate subject counselling will be made available by the investigator in the event of a positive finding. Notification of state and federal authorities, as required by law, will be the responsibility of the investigator. A copy of the lab report must be placed in the patient's file.

### **5.7.4 Latent tuberculosis infection screening**

Latent tuberculosis infection screening will be performed by a PPD skin test by intradermal injection of 5 tuberculin units of standard PPD, and/or interferon-gamma release assay such as Quantiferon-Gold assay at screening visit or within 6 months before patient study entry, and the results will be evaluated at screening visit before the first dose of study medication. A PPD skin induration at 72 hours of  $\geq 5$  mm is interpreted as a positive result. If PPD test or Quantiferon-Gold assay result shows latent TB infection without signs of active tuberculosis disease, patient will be allowed to enter the study in the study, if the patient is taking isoniazid prophylaxis before the study drug administration and agrees to continue the prophylaxis for 9 months.

Also because of natural life threatening course of neurological and vascular involvements, in patients who need an urgent intervention, drug administration can be started without waiting test results of PPD or Quantiferon assay if there are no findings of active tuberculosis disease. If but test results confirm a latent TB infection without signs of active tuberculosis, patients should start taking INH prophylaxis treatment for 9 months along with the study drug administration.

### **5.7.5 Chest X-ray**

In the event of a positive PPD skin test result at screening, or prior BCG immunization, or history of treated tuberculosis, a chest X-ray will be obtained, if one has not been administered during the 12 months before the first dose of study medication to assess the tuberculosis status of the patient. If a chest X-ray has been obtained in the previous 12 months, a chest X-ray may be ordered at the investigator's discretion, based on the patient's clinical picture and local standard of medical care. Any significant findings will be recorded in the "Relevant medical history/Current medical conditions" section of the CRF as necessary.

## **5.8 Treatment exposure and compliance**

Any deviations from the protocol regarding the administration of study medication must be described on the Dose Administration Record CRF.

Concomitant medications/ non-drug therapy before the first dose of study medication and after start of study drug will be collected, including medication name and reason.

## **5.9 Efficacy**

### **5.9.1 Resolution of Attacks**

#### **The definition of the attack**

**For Vascular Disease:** Recent Onset symptomatic Venous Thrombosis or Arterial Aneurysm.

**For Neurologic Disease:** An acute/subacute neurological syndrome including any of hemiparesis, ataxia, dysarthria within the first month of onset of neurologic manifestations.

**Primary endpoint:** Resolution of acute exacerbation findings related to BD based on achievements in any of the following items without deterioration on day 30:

#### **1-For Neuro Behcet Attack**

- A Improvement of muscle strength (Measured by MRC, and VAS)
- B Ataxia (Measured by global assessment of Physician)
- C Modified EDSS (Modified Expanded Disability Status Scale) , Neuro-Behçet's Disability Score (NBDS) **ranging from 0-8 and the modified Rankin scores (0-6)**
- D Improvement in systemic inflammatory findings (CRP, ESR, SAA)
- E Any decrease in the size of the MRI lesion, or disappearance of contrast enhancement

**Complete response** will be defined as full clinical recovery to pre-attack state, disappearance of MRI lesion(s), CSF becomes normal.

**Partial response** will be defined as partial improvement in clinical findings, but with findings still worse than pre-attack state, MRI lesions which become smaller with no or less enhancement, and a decrease in CSF cell count.

**Non-response** will be defined as no improvement in clinical findings, no change on MRI, no change in CSF parameters, or worsening in those findings.

## **2-For patients with large vessel vascular disease**

### A Improvement in relevant symptoms

- a. Localised pain (by using physician and patient's global assessment with visual analog scale (VAS))
- b. Abdominal pain, (by using physician and patient's global assessment with visual analog scale (VAS))
- c. Calf thickness, (by measuring)
- d. Hemoptysis (yes/no)

### B Improvement in systemic inflammatory findings (CRP, ESR, SAA)

### C Any improvement in radiological findings depending on the involved vessels (MR, CT or Doppler findings)

**Complete response** will be defined as clinical and laboratory improvement based on >50% improvements in patient's and physician's global assessments by using VAS, and >50% reduction in CRP values; along with stable or >20% reduced aneurysm size in patients with arterial involvement, and stable or >20% reduced calf swelling in patients with lower extremity venous thrombosis.

**Partial response** will be defined as clinical and laboratory improvement based on observing an improvement between 20-50% according to patient's and physician's global assessments by using VAS, 20-50% reduction in CRP values; along with stable or less than 20% reduced aneurysm size in patients with arterial involvement, and stable or less than 20% reduced calf swelling in patients with lower extremity thrombosis.

**Non-response** will be defined as observing no or less than 20% clinical improvement by patient's and physician's global VAS or worsening of clinical findings, no change or increase in acute phase response, increase in aneurysm size for patients with arterial involvement or progression of venous thrombosis in patients with venous involvement.

## **5.9.2 Preservation of Remission within 12 months :**

Investigators will question absence / presence of attack during each visit. Normalization of inflammatory markers, improvements in symptoms will be recorded during each visit.

### **5.9.3 Overall Disease Activity Measures**

Using Behcet Disease Current Activity Form (BDCAF) to collect general information about the disease course and progress. The patient will fill the form starting from baseline till the end of the study in every treatment day. The scores will be analysed at Day 30, 90, 180 and 360.

### **5.9.4 Steroid Tapering**

Prednisolone dosage should be 20 mg or less at baseline, and it should not be increased during the trial.

At the end of Day 30, complete responders begin to decrease the steroid doses. Tapering target will be 2,5 mg for every 2 weeks. At Day 120, patients expected to use prednisolone no more than 5 mg / day.

### **5.9.5 Improvement / Changes in Symptoms**

Headache; will be assessed by Visual Analog Scale, ranging from 0 to 10 cm, 0 indicating the best score and 10 the worst score, and it will be assessed by the patients and physicians during each visit.

Localized Pain; will be assessed by Visual Analog Scale, ranging from 0 to 10 cm, 0 indicating the best score and 10 the worst score, and it will be assessed by the patients and physicians during each visit.

Abdominal Pain will be assessed by Visual Analog Scale, ranging from 0 to 10 cm, 0 indicating the best score and 10 the worst score, and it will be assessed by the patients and physicians during each visit.

Ataxia Improvements / Changes will be assessed by Physician Global Assessment.

Calf thickness / swelling will be calculated by tape measure.

Hemoptysis will be assessed by (Yes / No) scale.

### **5.9.6 Imaging**

Different imaging techniques can be used for the assessment of vascular involvement depending on the localization and types of the involved vessels.

For Deep Vein Thrombosis, Doppler ultrasound investigation and/or MRI will be used.

For the assessment of arterial aneurysms, including pulmonary artery aneurysms, CT and/or MR imaging will be performed. [REDACTED]

For Neurologic Involvement, cranial MR imaging will be preferred. MR imaging is extremely useful in differentiating NBD from its mimics. The brainstem–thalamic–basal ganglia lesions, in the proper clinical context can strongly support the diagnosis of acute/subacute parenchymal NBD. [REDACTED]

## **5.10 Safety**

### **5.10.1 Physical examination**

A complete physical examination will be performed at all study visits. It 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.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions screen on the subject's CRF. Significant findings made after the start of study drug, which meet the definition of an AE must be recorded on the AE screen of the subject's CRF.

### **5.10.2 Vital signs**

Vital signs will be assessed at Screening, at all study visits. This will include measurement of subject's body temperature, blood pressure (BP) and pulse.

Body temperature will be measured by the investigator at each visit using established methods such as tympanic measurements. In addition, subject will measure the subject's body temperature (tympanic or axillary) during occurrence of fever and record it in the subject's diary if they experience fever.

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

### **5.10.3 Height and weight**

Height will be measured in centimeters at Screening.

Body weight (in indoor clothing, but without shoes) will be measured to the nearest 0.1 kilogram (kg) at , Screening, Visit 5, and Visit 15. Laboratory evaluations clinics laboratory will be used for analysis of all specimens collected except for CRP and urine dipstick as outlined in the laboratory test section.

The investigator will evaluate the clinical significance of each laboratory value outside of the reference range. This decision should be based upon the nature and degree of the observed abnormality. The investigator may choose to repeat any abnormal result ONCE, in order to rule out laboratory error. "NCS" will be entered on the original laboratory sheet to the right of all laboratory values, which are outside the reference range, but are judged "not clinically

significant." The physician making these assessments should date and initial each form. Values, which are considered clinically significant and/or study drug related will be noted on the respective Central Lab Assessment CRF page with reference to the date, study day, and hour if applicable. A copy of each laboratory report must be placed in the subject's file. Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis. Repeated evaluations are mandatory until normalization or until the change is no longer clinically relevant. In case of doubt, Novartis must be contacted.

#### **5.10.3.1 Hematology**

Haemoglobin, hematocrit, white blood cells (WBC) count with differential, red blood cells (RBC) count and platelet count will be evaluated at Visits 1,3,4,7,8,9,10, and 11

#### **5.10.3.2 Clinical chemistry**

Albumin, alkaline phosphatase, total bilirubin, indirect and direct reacting bilirubin, calcium, chloride, cholesterol, creatinine (with derivation of creatinine clearance value), CPK,  $\gamma$ -GT, glucose, LDH, inorganic phosphorus,  $\alpha$ -amylase, potassium, total protein, SGOT, SGPT, sodium, triglycerides, urea/BUN and uric acid will be evaluated at Visits 1,3,4,7,8,9,10 and 11

#### **5.10.3.3 Urinalysis**

Urine sample will be obtained for semi-quantitative 'dipstick' measurements of specific gravity, pH value, protein, glucose, bilirubin, ketones, leukocytes, and blood at Screening and all subsequent visits.

In case blood and/or leukocytes, and/or protein show traces/values in the 'dipstick' evaluation, a microscopic examination including RBC, WBC, and casts will be performed by the local laboratory. If casts are noted, the type is to be specified on the relevant local lab Assessment CRF (a note should be attached to the line referring to the urinalysis collection field).

#### **5.10.4 Electrocardiogram (ECG)**

A standard 12 lead ECG will be performed at Screening and End of Study Visit.

The investigator will review the ECG, sign and date the tracing, and record any significant findings in the CRF. The CRF will contain the ventricular rate, PQ or PR interval, QRS duration, QT interval (uncorrected) and the overall interpretation (normal, clinically insignificant abnormality, clinically significant abnormalities which need to be specified further).

Each ECG tracing should be labelled with the study number, patient initials, patient number, date, and kept in the source documents at the study site.

Clinically significant abnormalities at Screening should also be recorded on the relevant medical history/Current medical conditions CRF page.

### 5.10.5 Pregnancy and assessments of fertility

Canakinumab should not be given to pregnant women. Female subjects of child-bearing potential must undergo pregnancy testing throughout the study and need to agree to an effective method of contraception during the entire study and for at least 3 months after study completion. **Serum test and/or urine test are mandatory for pregnancy at the screening visit for woman .** Other assessments

### 5.10.6 CSF Collection

CSF analyses that were performed within 3 weeks before the study entry could also be used. CSF cell count analysis will be performed in the local laboratory [REDACTED]

Each CSF sample will consist of 1 mL to be collected in a sterile polypropylene tube that contain no preservatives. After collection, the sample may be stored at 4°C. However, it must be processed to centrifugation within 1 hour of the lumbar puncture. Longer storage times at 4°C must be documented accordingly in the source documents and CRF. [REDACTED]

Sample tubes are centrifuged at 4000 x g for 10 minutes at 4°C to pellet cells and other insoluble material. The supernatant is then transferred to a new sterile polypropylene tube and gently mixed by inversion. Two (2) aliquots (0.5 mL) of the supernatant are dispensed to 0.5 mL polypropylene cryovials. This procedure limits oxidation effects by minimizing empty space in the cryovials. The 0.5 mL cryovials containing the CSF aliquots as well as the polypropylene tubes containing the cell pellets are immediately placed on dry ice.

Once completely frozen, the tubes are transferred to a freezer for storage below -70°C until shipment to the central lab. The samples must be packed on sufficient dry ice for shipment to the central lab without thawing. Upon arrival at the central lab, CSF samples must be stored below -70°C. Any thawing of frozen samples must be avoided.

Sampling problems will be noted in the CRF as an attached note.

### 5.10.7 Pharmacokinetics

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. It is important to note that the volume of blood sampling will be adapted to the age of the child according to clinical practice at the investigator site. For each scheduled PK sample, 2 mL of blood will be drawn into a plain barrier tube to obtain 1 ml serum. The sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. The sample will be split into two aliquots to be transferred into polypropylene screw-cap tubes. Serum tubes will be frozen within 90 min of venipuncture and kept at  $\leq -18^{\circ}\text{C}$  pending analysis. One of the two serum samples is to be kept at the study site as a backup while the other one will be shipped to the analytical center.

Time points for canakinumab PK sample collection at Visits:

- Day 0 (Visit 1)
- Day 7 (Visit 2)
- Day 30 (Visit 4); pre-dose
- Day 60 (Visit 5); pre-dose
- Day 90 (Visit 6) pre-dose
- Day 180(Visit 9) pre-dose
- Day 240(Visit 11) pre-dose
- Day 360 (Visit 15) pre-dose

#### **5.10.7.1 Analytical method(s)**

Analytes, media and methods: canakinumab in serum by competitive ELISA, limit of quantification (LOQ) at 100 ng/mL.

Details of the analytical methods to assess canakinumab in serum will be described in the bioanalytical data report.

#### **5.10.7.2 PK sample handling, labeling and shipment instructions**

##### **5.10.7.2.1 Sample labeling**

Serum tubes will be used to collect samples.

The samples for the pharmacokinetic profile will be labeled as follows:

PK

Study Code: CACZ885NTR01

Subject Number:

Sample Number:

Date / Study Day:

Labels will be provided to the investigator with all label information preprinted on the label.

The actual sample collection date and exact time will be entered on the PK Blood Collection

Log CRF page. Sampling problems will be noted on the PK Blood Collection Log CRF

##### **5.10.7.2.2 Shipment of pharmacokinetic samples to Central Laboratory**

For each shipment, all pharmacokinetic samples are to be entered in the shipping log which can be found in the central laboratory manual. The original document will be retained at the site in the Investigator's file, and a copy of the PK Samples Shipping Log page must be included with the package of PK samples shipped.



- Day 360 (Visit 15); pre-dose

All PK/PD samples will be shipped to the following vendor:

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
phone [REDACTED]  
fax [REDACTED]

#### **5.10.8.2 Analytical method(s)**

Total IL-1 $\beta$  will be analyzed in serum by means of a competitive ELISA assay, limit of quantification at 1.00 pg/mL.

##### **5.10.8.2.1 Sample labeling**

Serum tubes will be used to collect samples.

The samples for the pharmacodynamic profile will be labelled as follows:

PD

Study Code: CACZ885NTR01

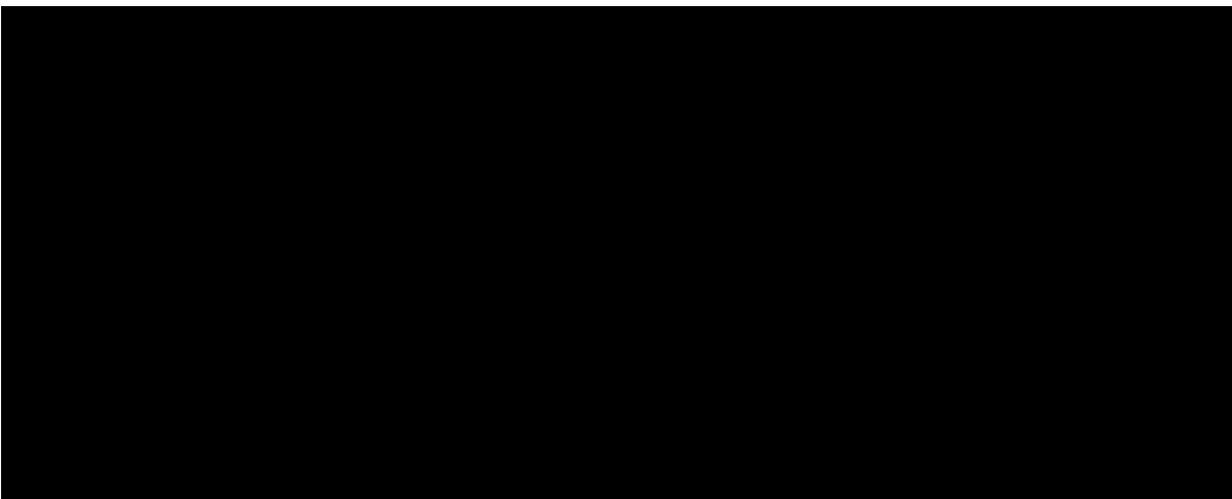
Subject Number:

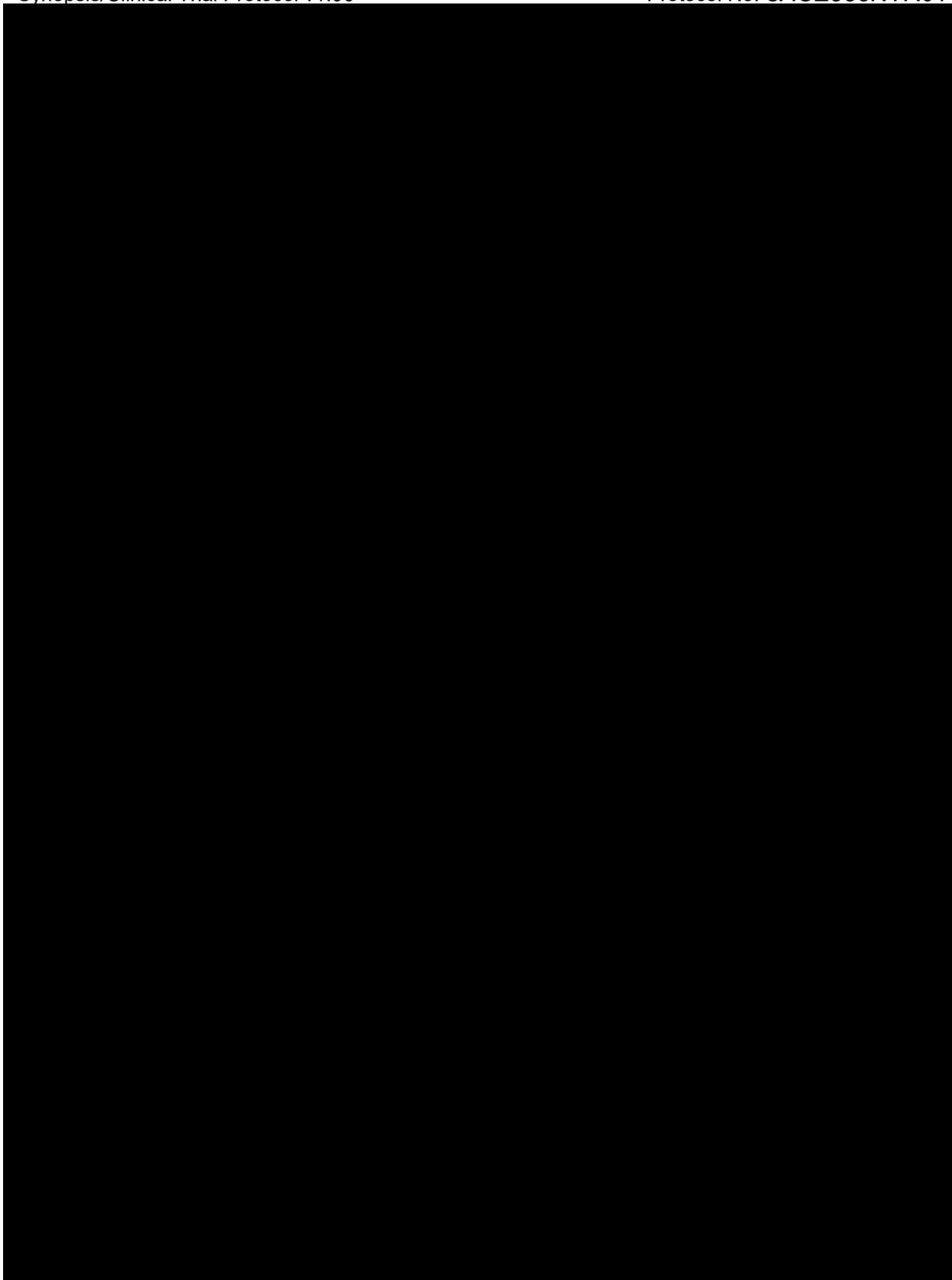
Sample Number:

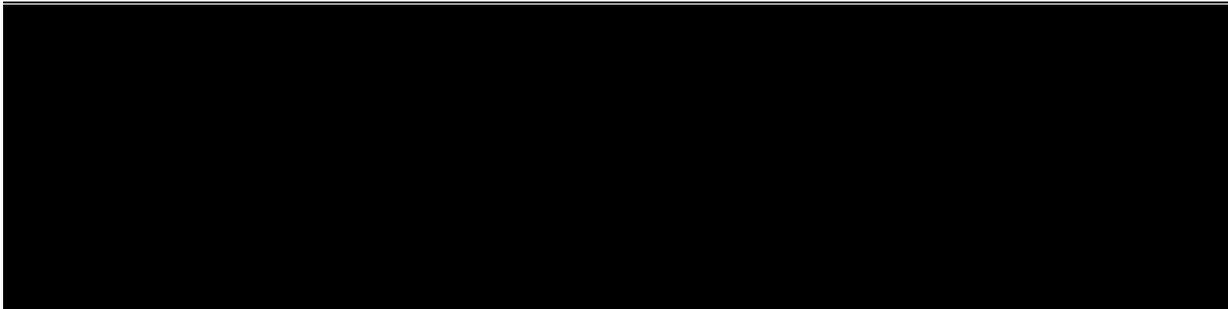
Date / Study Day:

Labels will be provided to the investigator with all label information pre-printed on the label. The actual sample collection date and exact time will be entered on the PD Blood Collection CRF page. Sampling problems will be noted on the PD Blood Collection Log CRF (a note should be attached to the line referring the PD blood collection field).

For each shipment, the same procedure described above has to be followed.







## 6 Safety monitoring

### 6.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavourable 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 fulfil at least one of the following criteria:

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

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

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 investigational treatment (no/yes), or

- 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)
- action taken regarding investigational treatment
- whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

## 6.2 Serious adverse events

### 6.2.1 Definition of SAE

An SAE is 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
  - 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 to prevent one of the outcomes listed above.

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

**Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.**

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/investigational] (*select*) treatment dosage adjusted/temporarily interrupted; study drug(s) permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

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 investigational 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 Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

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

### **6.2.2 SAE reporting**

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days *following the last administration of study treatment* 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 *each specific component of study treatment (if study treatment consists of several drugs)* 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 treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same

investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Local Novartis Turkey Drug Safety Department will report all suspected unexpected serious adverse reactions (SUSARs) to Ministry of Health as per The Regulation on Clinical Trials and Guidance on the collection, verification and submission of Adverse Event/Reaction Reports Occurring During Clinical Trials of Medicinal Products and Biological Products

### **6.3 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 [investigational/study treatment] (*select*)

Any SAE experienced during pregnancy must be reported on the SAE Report Form.

### **6.4 Prospective suicidality assessment**

The Columbia-Suicide Severity Rating Scale (C-SSRS), a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior using a semi-structured interview to probe patient responses, has to be administered at each visit, including unscheduled ones.

If at any assessment after screening and/or baseline the score is 4 or above on the Suicidal Ideation item or any “yes” on the Suicidal Behavior item, the patient **must** be referred to a health care professional for further assessment and/or treatment. The decision on whether the study treatment should be discontinued is to be taken by the health care professional to whom the patient is referred to.

## **7 Data review and database management**

### **7.1 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, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that investigational 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.

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.

## **7.2 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. *CRO working on behalf of Novartis* by field monitors or by the investigational site, with one copy being retained at the investigational site. Once the CRFs are received by *CRO working on behalf of Novartis*, their receipt is recorded, the original copy is placed in Central Files, and the non-carbon-required copy is forwarded to the responsible Data Management staff for processing.

## **7.3 Database management and quality control**

Data from the CRFs are entered into the study database by CRO using double data entry. Verification is performed manually by a separate member of the Data Management staff by comparing the Case Report Form to the data entered into the database.

Data from the CRFs are entered into the study database by Data Management staff using double data entry and by referring to the scanned image of the CRF

Data from the CRFs are entered into the study database by Contract Research Organization (CRO) staff following their own internal standard operating procedures that have been reviewed and approved by Novartis.

Subsequently, the entered data are systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Other errors or omissions are entered on Data Query Forms, which are returned to the investigational site for resolution. The signed original and resolved Data Query Forms are kept with the CRFs at the investigator site, and a copy is sent to Novartis so the resolutions can be entered into the database. Quality control audits of all key safety and efficacy data in the database are made prior to locking the database.

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

Laboratory samples will be processed by institute and the results will be sent electronically to Investigator.

ECG readings will be processed by investigators and results will be recorded .

#### **7.4 Data Monitoring Committee**

Not required.

#### **7.5 Adjudication Committee**

Not required.

### **8 Data analysis**

#### **8.1 Analysis sets**

Investigators will enter the information required by the protocol into the Novartis Case Report Forms (CRFs). Non-obvious errors or omissions will be entered on Data Query Forms, which will be returned to the investigational site for resolution.

The data from all centers will be pooled and summarized with respect to demographic and baseline characteristics and efficacy and safety observations. [REDACTED]

[REDACTED] Data will be presented for the complete intent-to-treat population (all subjects having taken at least one dose of study medication) as well as the per-protocol population (all subjects who completed the study without major protocol deviations). Safety data will be evaluated for the safety population (all subjects having taken at least one dose and who have at least one post-baseline assessment).

Data summaries will be presented.

This trial is an exploratory study, and it is not powered for a statistical analysis. The statistical analyses of the measurements will be performed when possible, and these analysis will be done by the investigators and an independent Contract Research Organization.

#### **8.2 Patient demographics and other baseline characteristics**

Demographic and baseline characteristics will be summarized descriptively for the safety population. Continuous variables will be summarized by mean, standard deviation, median, minimum, maximum, and number of subjects with non-missing data. Categorical variables will be summarized by absolute frequencies and percentages.

#### **8.3 Treatments**

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

## **8.4 Analysis of the primary variable(s)**

### **8.4.1 Variable(s)**

Percentage of complete responders.

Symptoms measured by VAS.

Percentage of patients achieved appropriate steroid tapering.

Changes of general disease activity measured by BDCAF.

### **8.4.2 Statistical model, hypothesis, and method of analysis**

To claim the efficacy of canakinumab on the resolution of attacks, at least 50% response will be aimed in at least 50% of the patients.

All parameters will be compared with baseline values. Complete / Partial / Non responders definitions can be seen in efficacy assessment section.

## **8.5 Analysis of secondary variables**

### **8.5.1 Efficacy variables**

Kaplan-Meier estimates will be presented for time to relapse.

Continuous endpoints (steroid tapering, VAS scores, BDCAF scores) will be summarized by mean, standard deviation, median, median, interquartile range, minimum and maximum.

Differences between pre-treatment and post-treatment values will be analysed by the non-parametric Wilcoxon signed rank test at the 0.05 level of significance.

Correlations between the different parameters will be explored by Spearman's rank correlation coefficient.

Categorical variables will be summarized by absolute frequencies and percentages.

### **8.5.2 Safety variables**

The assessment of safety will be based mainly on the frequency of adverse events, which includes all serious adverse events. Adverse events will be summarized by the number and percentage of subjects having any adverse event, having an adverse event in each body system and having each individual adverse event. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

Newly occurring notable laboratory values and newly occurring vital sign abnormalities will be tabulated. Listings with abnormalities flagged will be provided

### **8.5.3 Pharmacokinetics**

A mixed effects modeling approach will be taken in order to analyze the complete PK data from the study. Quality of individual fits to the dataset will be assessed and if the fits are apparently unbiased, the model derived population pharmacokinetic model parameter mean and inter-individual variance-covariance matrices of parameters such as CL (clearance), V

(apparent volume of distribution),  $k_a$  (first-order absorption rate constant) and withinindividual variance will be estimated. In addition, posthoc estimates of the same parameters, i.e. CL, and V will be reported for each individual.

## **8.6 Interim analyses**

There will be statistical analysis at Day 30 , Day 90, Day 180 and Day 360.

## **8.7 Sample size calculation**

Because of exploratory nature of the study, 10 patients will provide information.

# **9 Ethical considerations**

## **9.1 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 with the ethical principles laid down in the Declaration of Helsinki.

## **9.2 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 HA/EC, and a copy of the approved version must be provided to the Novartis monitor after HA/EC 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.

### **9.3 Responsibilities of the investigator and IRB/IEC**

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted HA Ethics Committee before study start. A signed and dated statement that the protocol and informed consent have been approved by the HA/EC 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, HA/ECs, 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.

### **9.4 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](http://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 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.

### **10.1 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 HA/EC. 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.



### 13 Appendix 1: Blood collection Log

The volume of blood to be collected for lab parameters that will be analyzed by the central laboratory can be found in the central laboratory manual. The blood collection logs for PK/PD [REDACTED] samples are shown in Table 13-1.

**Table 13-1 Blood Collection Log for PK/PD [REDACTED] Samples**

Day	Pharmacokinetics			Pharmacodynamic	
Analyte/purpose	Canakinumab			Total IL-1 $\beta$	
	PK Collection No.	Sample No.	mL	Number	mL
Day 0	1	1	2	101	3
Day 7	2	2	2	102	3
Day 30	3	3	2	103	3
Day 60	4	4	2	104	3
Day 90	5	5	2	105	3
Day 180	6	6	2	106	3
Day 240	7	7	2	107	3
Day 360	8	8	2	108	3