A randomized, double-blind, placebo controlled, withdrawal study of flare prevention of canakinumab (ACZ885) in patients with Systemic Juvenile Idiopathic Arthritis (SJIA) and active systemic manifestations

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The primary objectives of this study are:Part II: to demonstrate that the time to flare in Part II is higher with canakinumab than with placebo.Part I: to assess if canakinumab allows tapering of steroids as per protocol in at least 25% of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON35648

Source
ToetsingOnline

Brief title
*-SPECIFIC 2

Condition

- Autoimmune disorders

Synonym
inflammation of the joints, rheumatism

Research involving

Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Door de farmaceut zelf (Novartis Pharma)

Intervention

Keyword: canakinumab (ACZ885), Efficacy, placebo-controlled, SJIA (Systemic Juvenile Idiopatic Arthritis)

Outcome measures

Primary outcome

The primary efficacy variable for Part I is the proportion of patients who were

on steroids at entry into Part I and who were able to taper steroid as per

protocol.

The primary efficacy variable is the time to flare in Part II.

Secondary outcome

1. Maintenance of adapted ACR Pediatric 30/ 50/ 70/ 90/ 100 criteria during

Part II

2. Change in disability over time by CHAQ©

3. Change in HRQoL over time by CHQ-PF50©

4. Proportion of patients who reached a steroid dose * 0.2 mg/kg at end of Part

Ic

5. Steroid level at end of Part Ic and change from baseline to end of Part Ic

6. Proportion of patients achieving the adapted ACR Pediatric 30/50/70/90/100

criteria in

Part I

7. proportion of patients who have body temperature *38°C at Day 3 in

Part I

8. Time to adapted ACR Pediatric 50 criteria and normal CRP (<10mg/L) in Part I

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9. Time to adapted ACR Pediatric 70 criteria and normal CRP (<10mg/L) in Part I

Part I:

* Changes in health-related quality of life will be measured using EQ-5D and PDSS.

Part II:

* Time to inactive disease:

* Frequency and percentage of patients who meet the definition of inactive disease on medication as defined by Wallace, Ruperto, and Giannini (2004) will be presented.

* Changes in health-related quality of life will be measured using EQ-5D and PDSS.

* Summary statistics of changes from baseline in joint erosions in the hand and wrist will be presented by overall exposure to study drug.

* Growth velocity:

* Tanner stages will be summarized descriptively by visit and listed.

-Safety, tolerability, pharmacokinetics, pharmacodynamics, pharmacogenomics, pharmacogenetics and exploratory biomarker analyses.

Study description

Background summary

Systemic Juvenile Idiopathic Arthritis (SJIA) is a unique subset of Juvenile Idiopathic Arthritis (JIA) that occurs in children 16 years of age and younger, and accounts for approximately 4 - 17 % of JIA (Ravelli and Martini 2007). The peak age of disease onset lies between 18 months and 2 years (Symmons, et al 1996), but SJIA may occur in children of any age and, rarely, in young adults too (Woo 2006).
Canakinumab, as a potent neutralizer of IL-1*, is expected to treat the underlying structural features of arthritis (inflammation, bone and cartilage degradation), as well as providing relief of the symptoms in at least a subset of patients with these forms of arthritis.
Preliminary data from the phase II ongoing trial indicate that 13/22 patients (59%) responded to canakinumab achieving at least an adapted ACR pediatric 50 after 15 days. In 4 cases inactive disease status was reached (no joints with active arthritis, no fever, normal CRP and no disease activity according to physician*s assessment).

Based upon the encouraging preliminary results from POC/phase II, Novartis believes that it has a responsibility to evaluate canakinumab as a safe and efficacious treatment option for children with SJIA.

Study objective

The primary objectives of this study are:
Part II: to demonstrate that the time to flare in Part II is higher with canakinumab than with placebo.
Part I: to assess if canakinumab allows tapering of steroids as per protocol in at least 25% of the
patients.
Secondary objectives of this study are:
Part II:
* To evaluate the maintenance of efficacy (length of time that patients continuously maintain or
improve their adapted ACR Pediatric 30/ 50/ 70/ 90/ 100 criteria reached at entry into Part II)
of canakinumab as compared to placebo
Part I:
* To evaluate number of patients who have reached a steroid dose * 0.2 mg/kg at end of Part
Ic
* To evaluate the level of steroid tapering achieved at the end of Part Ic
* To evaluate the efficacy (percentage of patients who meet the adapted ACR

Pediatric 30/ 50/
70/ 90/ 100 criteria) of canakinumab in Part I
* To evaluate the efficacy of canakinumab based percentage of
patients who have body temperature * 38°C) at Day 3 in Part Ia
* To evaluate time to adapted ACR Pediatric 50 criteria and normal C-Reactive
Protein (CRP
<10 mg/L) during Part I
* To evaluate time to adapted ACR Pediatric 70 criteria and normal CRP (<10
mg/L) during
Part I
Parts I and II:
* To evaluate the change in disability over time by use of the cross culturally
adapted and
validated version of the Child Health Assessment Questionnaire (CHAQ©)
* To evaluate the change in Health-Related Quality of Life (HRQoL) over time by
use of the
cross culturally adapted and validated version Child Health Questionnaire (CHQ)
* To evaluate the safety, tolerability and immunogenicity of canakinumab
* To evaluate the pharmacokinetics (PK) / pharmacodynamic (PD) of canakinumab
Exploratory objectives of this study are:
Part II:
* To explore the time to inactive disease
* To explore the percentage of patients who will meet the definition of
inactive disease on
medication as defined by Wallace, Ruperto, and Giannini (2004)
* To explore the progression of joint erosions in the affected hand and/or
wrist by x-ray in a
subset of volunteer patients
Parts I and II:
* To explore the change in HRQoL over time by use of the EuroQoL Five Dimension
Questionnaire (EQ-5D) (for patients * 12 years of age) or EQ-5D proxy (for
patients 8 - 11
years of age)
* To explore the impact of treatment with canakinumab on sleepiness in children
over time by
use of the Pediatric Daytime Sleepiness Scale (PDSS)
* To explore the impact of treatment with canakinumab on growth velocity
* To explore the impact of treatment with canakinumab on physical development
in children,
and adolescents from ages 6 * 20 by use of the Tanner stages scale
* To explore the protein, mRNA and DNA biomarkers (e.g. HLA-DQA1) in order to
identify
retrospectively responder/non-responder patients

Study design

Study design:

This is a two-part study with an open-label, single-arm active treatment in Part I followed by a
randomized, double-blind, placebo controlled, event-driven withdrawal design in Part II.
No interim analysis is planned.
Part I (Open-label treatment period):
Part I is an open-label, active treatment period to identify
canakinumab-treated patients who meet the
adapted ACR Pediatric 30 criteria at Day 15 and to allow for these patients to taper their steroid dose.
The maximum duration of Part I will be 32 weeks, corresponding to maximum 8 injections of
canakinumab. Part I is separated into 4 subparts Ia to Id. While subparts Ia and Ib aim to induce and
maintain an at least adapted ACR Pediatric 30 response without steroid tapering, subpart Ic aims to
reduce steroid dose to the lowest possible dose prior to the potentially long duration of Part II and to
evaluate steroid tapering in responders. Subpart Id is designed to stabilize patients on an achieved
steroid dose before entering the withdrawal Part II.
An Interactive Voice Response System (IVRS) will be used in Part I to identify the treatment to be
prepared and administered.
Part Ia
Once patient eligibility is confirmed at screening, patients will enter Part Ia and receive the first
subcutaneous (s.c.) injection of canakinumab (4 mg/ kg) on Day 1. The duration for Part Ia is 4 weeks.
Rule for rolling over patients from study CACZ885G2305 and CACZ885A2203 into Part Ia:
* Placebo patients who did not clinically improve with study treatment, as per investigator*s
discretion, between Day 3 and Day 15 during the study CAZ885G2305 will be allowed to roll
over into study CACZ885G2301: They will start their participation in study CACZ885G2301 at
Day 1, i.e. no screening visit will be required for those patients.
* Placebo patients who did not meet the adapted ACR Pediatric 30 criteria at Day 15 in study
CAZ885G2305 will be allowed to roll over into study CACZ885G2301: They will start their
participation in study CACZ885G2301 at Day 1, i.e. no screening visit will be required for
those patients.
* Placebo-treated patients who achieves a minimum adapted ACR Pediatric 30 response at

Day 15 but clinically deteriorates between Day 15 and Day 29 during study CACZ885G2305
and intervention is deemed necessary by the investigator will be allowed to roll over into study
CACZ885G2301: They will start their participation in study CACZ885G2301 at Day 1, i.e. no
screening visit will be required for those patients.
* Patients from the study CACZ885A2203 will enter the CACZ885G2301 study when they
would receive the next dose of canakinumab in protocol CACZ885A2203. They will need to
be screened prior to entry.
Steroids will be maintained stable for the full duration of Part Ia. No tapering of steroids is allowed in
Part Ia.
At Day 1, Physician*s Global Assessment of disease activity on a 0-100 mm VAS, CHAQ©, CHQPF50
©, EQ-5D, PDSS, number of joints with active arthritis using the ACR definition, number of joints
with limitation of motion, laboratory measure of inflammation: CRP (mg/L) and assessment of
intermittent fever due to SJIA (oral or rectal body temperature > 38°C only for several hours during the
day) during the preceding week will be assessed.
All patients with an affected hand and/or wrist who consent at baseline (Day 1) (volunteer patients) will
be subjected to an articular x-ray. The x-ray film will be sent to a Clinical Research Organization
(CRO) for confirmation of the quality. Assessment of the x-ray film will be performed by an
independent x-ray reading committee.
At Day 3 clinical response will be assessed as per Physician*s Global Assessment of disease activity,
number of joints with active arthritis, number of joints with limitation of motion, CRP, and body
temperature.
At Day 15, clinical response will be assessed as per adapted ACR Pediatric 30 criteria, i.e.
improvement from baseline of at least 30% in at least three of the six response variables and no
intermittent fever (i.e. body temperature * 38°C) in the preceding week, with no more than one of the
remaining variables worsening more than 30% (see Section 7.4.1).
Patients who meet the adapted ACR Pediatric 30 criteria at Day 15 will continue in the study.
Patients who do not meet the adapted ACR Pediatric 30 criteria at Day 15 will be discontinued from

the study, will complete Visit 5 (Day 29) assessments, and will be treated as per standard local
medical practice but will be followed-up for safety for 2 months after the last injection.
Patients who do not maintain a minimum adapted ACR Pediatric 30 response between Day 15 and
Day 29 during Part Ia will complete Visit 5 (Day 29) assessments, be withdrawn from Part Ia, and may
enter the extension study CACZ885G2301E1. Physician and family have the option to continue
treatment with canakinumab if it is thought to be beneficial to the patient.
At Day 29, clinical response as per adapted ACR Pediatric criteria will be assessed.
During Part Ia, efficacy, safety and tolerability assessments will be performed at all visits.
Any patient who discontinues Part Ia and does not enroll into the extension study CACZ885G2301E1
will be followed up for safety for 2 months after the last injection.
Part Ib
Patients completing Ia will enter Part Ib on Day 29 if they continue to meet at least adapted ACR
Pediatric 30 criteria. The duration for Part Ib is 4 weeks.
Rule for rolling over patients from study CACZ885G2305 into Part Ib:
* Canakinumab patients who completed CACZ885G2305 and continue to meet at least adapted
ACR Pediatric 30 criteria will be allowed to roll over into study CACZ885G2301: They will start
their participation in study CACZ885G2301 at Day 29, i.e. no screening visit and no Part Ia visits
at Days 1, 3, and 15 will be required for those patients.
Steroids will continue to be maintained stable for the full duration of Part Ib. No tapering of steroids is
allowed in Part Ib.
At Day 29, all patients will receive an injection of study drug (canakinumab) and clinical response will
be assessed as per adapted ACR Pediatric criteria.
At Day 57, clinical response will be assessed as per adapted ACR Pediatric criteria.
Patients who do not maintain a minimum adapted ACR Pediatric 30 response between Day 29 and
Day 57 during Part Ib will be withdrawn from Part Ib, will complete Visit 6 (Day 57) assessments and
may enter the extension study CACZ885G2301E1 at the physician*s and family*s discretion.
During Part Ib, efficacy, safety and tolerability assessments will be performed at Day 29 and Day 57.
Part Ic (Steroid tapering)

Patients completing Ib on Day 57 will continue into Part Ic if they meet at least an adapted ACR
Pediatric 30 criteria. Corticosteroid use is encouraged to be tapered down to the lowest possible dose
during Part Ic prior to entry into the potentially long duration of Part II.
The maximum duration of Part Ic
is 20 weeks. The objective of Part Ic is to evaluate canakinumab*s ability to allow patients to taper
down their steroid dose.
Patients who are unable to reduce their steroid dose to the predefined minimum dose in order to
qualify for Part Id and Part II by Day 197 (End of Part Ic) will be discontinued from the study, complete
End of Part Ic assessments and may enter the extension study CACZ885G2301E1.

Patients who are able to taper off of steroids prior to completing the maximum 20 weeks duration of
Part Ic and still maintain a minimum adapted ACR Pediatric response of 50 or higher should complete
their end of Part Ic assessments (Visit 11) at their next dosing visit and continue into Part Id.

During Part Ic patient will return to study site every 4 weeks to receive the next injection of
canakinumab and clinical response will be assessed as per adapted ACR Pediatric criteria. Efficacy,
safety and tolerability assessments will be performed at all dosing visits.
Part Id
Patients will enter Part Id at the time of their next canakinumab dose after they have completed Part Ic
successfully. Patients who are steroid free at study entry should enter directly into Part Id after
completing Part Ib without entering and completing Part Ic. The duration of Part Id is 4 weeks.
Patient will receive their next dose of canakinumab upon entry into Part Id and clinical response as per
adapted ACR Pediatric criteria will be assessed. Efficacy, safety and tolerability assessments will be
performed at the dosing visit.
Any patients on steroid will need to maintain stable dose for the full duration of Part Id. No tapering of
steroids is allowed in Part Id.
Patients who do not maintain a minimum adapted ACR Pediatric 30 response during Part Id will be
withdrawn from Part Id, will complete End of Part Id assessments and may enter the extension study
CACZ885G2301E1 at the investigator*s and family*s discretion.

The purpose of Part Id is to ensure that all patients have been treated with canakinumab for at least 12
weeks before entering Part II and that patients who have tapered and are still on steroids are on stable
steroid dose for at least 4 weeks before entering Part II.
Part II (Withdrawal period)
In Part II, the sustained efficacy of canakinumab will be assessed in a double-blind, randomized,
placebo-controlled, event-driven design with respect to the incidence of patients who flare.
The study will be stopped when the required number of 37 flares has occurred. Patients who
discontinue the study while in Part II will be counted as flares unless they discontinued because of
inactive disease for at least 24 weeks in Part II.
At start of Part II visit, patients who have sustained response to treatment with canakinumab according
to the adapted ACR Pediatric 30 criteria and have achieved a stable oral prednisone (or equivalent)
dose of * 0.5 mg/kg at the end of Part I will be randomized to either canakinumab or placebo in a ratio
of 1:1 and will receive an s.c. injection of study drug (canakinumab 4 mg/ kg or placebo).
Randomization will be stratified by prednisone (or equivalent) dose at the end of Part I (two strata: *
0.4 mg/kg, > 0.4 mg/kg) and degree of adapted ACR Pediatric response reached at the end of Part Id
(two strata: > adapted ACR Pediatric 50 criteria met (e.g. 70/90/100), * adapted ACR Pediatric 50
criteria met (e.g. 30/50)).
Steroids will be maintained stable for the first 24 weeks participation in the double-blind Part II. No
tapering of steroids is allowed during this first 24 weeks.

Patients who are on * 0.2 mg/kg oral prednisone (or equivalent) in Part II must continue to maintain
their steroid dose after the first 24 weeks in Part II until study completion (i.e. no steroid tapering is
allowed for the full duration of Part II).
Patients who entered Part II with an oral prednisone (or equivalent) dose > 0.2 mg/kg and * 0.5 mg/kg,
and who do not flare after at least 24 weeks participation in Part II may restart tapering their steroid.
During Part II patient will return to study site every 4 weeks to receive the next injection of study drug
(canakinumab or placebo) and clinical response will be assessed as per adapted ACR Pediatric

criteria. During Part II, efficacy, safety and tolerability assessments will be performed at all dosing
visits.
It is estimated that approximately 15 volunteer patients with an affected hand and/or wrist and who
consented at baseline (volunteer patients) will be subjected to an articular x-ray of both (left and right)
hands and wrists at End of Part II visit provided there is already a baseline x-ray available.
All patients who flare at any time during Part II, regardless if due to steroid tapering, will be withdrawn
from Part II, complete End of Part II assessments, and may enroll into the extension study
CACZ885G2301E1 at the investigator*s and family*s discretion.
Patients who maintained a status of inactive disease for at least 24 weeks during Part II may be
discontinued from the trial and will not be considered as having flared in the primary analysis. These
patients may enter the extension study CACZ885G2301E1 (e.g. to taper their steroid).
Premature Patient Withdrawal (PPW) will occur when patients discontinue from the study at any time.
Patients will complete the study when the required number of 37 flares has occurred during Part II.
At the End of Study, an open-label extension study of at least 2 year duration is planned to allow
patients to continue treatment with canakinumab until the product has been launched or until patients
have reached clinical remission and canakinumab can be discontinued (whichever occur first).
Novartis intends to launch the product worldwide. In case a launch in a country is for whatever reason
not possible, a compassionate use or maintenance protocol will be provided by Novartis. In case
Novartis decides due to an emerging unfavourable benefit/risk profile or are asked by Health
Authorities to stop the development of canakinumab the compassionate use or maintenance protocol
program cannot be pursued.

Intervention

Investigational and reference therapy:
Patients will be dosed every 4 weeks:
* Part I: a single dose of canakinumab (4 mg/kg)
* Part II: canakinumab (4 mg/kg) or placebo in a 1:1 ratio
The maximal total single dose of canakinumab allowed is 300 mg.

Note: Any patient who requires a dose greater than 150 mg (patients > 37.5 kg) will require two s.c. injections.

Study burden and risks

Risks and inconveniences
Risks are possible side effects of the study medicine or another medicine. Risks are also possible side effects that result from taking blood. If you were taking medication that made your symptoms of SJIA better or go away completely and you had to stop this medication to take part in the study, stopping this medication may cause these symptoms to come back. Your study doctor will discuss this more with you. The tests done at each visit are standard medical tests, however they may cause some discomfort. For example you will be asked to give some blood, which can also make you feel a bit faint or sick. It can also be uncomfortable and cause bruising. Rarely, a small blood clot or infection could occur at the site where the blood was taken, but this does not happen very often at all. When you have your blood pressure taken, the blood pressure cuff may feel a little tight and might cause a small bruise on your arm. When you are given a dose of canakinumab or placebo this will be injected just under the skin and may cause light pain, redness, bruising or itching. The testing to see if you already have tuberculosis may cause some swelling and hardness at the injection site. You will also be asked to have an ECG. This is a test of your heart which does not hurt. However the skin may become a little itchy and red where the sticky pads are placed. There is no radiation used during the ECG procedure. If you need a chest x-ray you will be given a very small amount of radiation. This can carry very small risks but the dose of radiation in a chest x-ray is very low.
The sonography is a painless test to have a picture of your liver and spleen. If your joints are inflamed, the assessment of your joints by your doctor may cause slight pain.

Side effects of study drug, canakinumab:
The study drug may involve risks that are currently unknown. Twenty clinical studies with canakinumab have been started; approximately 700 patients (including 43 children 4 years and above) have been treated with canakinumab (as of
December 2008 with several studies currently ongoing). Canakinumab was well tolerated. Canakinumab treatment discontinuations were rare. The maximum average duration patients have been on canakinumab is currently 2 1/2 years. In clinical trials, infections, mainly of the upper airways and in some instances serious, have been reported more frequently with patients taking canakinumab than with placebo (sugar pill). No unusual or opportunistic infections were reported and all infections that were
reported responded normally to standard therapy. The risk for the development of cancer with medications that inhibit the protein Interleukin-1, including canakinumab, is unknown, but can not be excluded entirely. A temporary spinning sensation (vertigo) has been reported in some patients soon

after they begin canakinumab therapy. It usually did not require treatment and resolved without problem
or interruption of their canakinumab treatment. There were serious events (or bad events). A *serious adverse event* is a side effect that may
be life-threatening or may require a study participant to be hospitalized for a time, it may or may not be related to a study drug.
Preliminary findings from an ongoing study with 23 SJIA patients show that the most common adverse events were upper respiratory tract infections. There were 17 serious adverse events where the patients were hospitalized. Eleven of these events were due to
other underlying medical history of the patients (irritated stomach (twice) ,hip arthritis, bleeding rectal skin lesion, abdominal pain from constipation with rectal bleeding, suspected pericarditis, worsening of SJIA (twice), pain and fear, tendonitis and
blood in the urine). Six of these events were infections leading to hospitalization (acute
tonsillitis, severe sore throat, flu-like viral illness, stomach virus with mild bleeding abnormality, hepatitis and severe nail infection).. All of these events resolved while continuing canakinumab treatment.
Serious events occurring more than once and suspected to be related to canakinumab iIn all
previous and ongoing studies of approximately 670 patients who do not have SJIA: vertigo (dizziness) (twice), nausea (twice) and vomiting (twice).
Mild skin inflammations at the injection site were reported by a few patients.

Allergic reactions
Sometimes people have allergic reactions to drugs. Most allergic reactions to drugs like canakinumab occurred within 2 hours after dose administration. Serious allergic reaction which may include low blood pressure, trouble breathing, seizures and death may occur. However, most reactions seen were mild to moderate. Some things that can happen during an
allergic reaction are: a rash, itching, having a hard time breathing, wheezing when you breathe, sudden drop in blood pressure, swelling around the mouth, throat or eyes, fast pulse, fever, sweating, and chills. There is a risk that a rare or previously unknown side effect will occur.

Other treatments
You do not have to be in this study to receive treatment for your SJIA. You may receive the standard therapy for SJIA which may include corticosteroids.

Benefits of treatment
You may receive no direct benefit from being in this study. However, your taking part may help patients get better care in the future.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Parent*s or legal guardian*s written informed consent and child*s assent, if appropriate, or patient*s informed consent for * 18 years of age before any study related activity is performed.
2. Male and female patients aged * 2 to < 20 years at the time of the screening visit
3. Confirmed diagnosis of SJIA as per ILAR definition (Petty, et al 2004) that must have occurred at least 2 months prior to enrollment with an onset of disease < 16 years of age:
* Arthritis in one or more joints with or preceded by fever of at least 2 weeks duration that is documented to be daily/ quotidian for at least 3 days and accompanied by one or more of the following:

* Evanescent nonfixed erythematous rash,
* Generalized lymph node enlargement,
* Hepatomegaly and/ or splenomegaly,
* Serositis
4. Active disease at the time of enrollment defined as follows:
* At least 2 joints with active arthritis (using ACR definition of active joint) (Not required for CACZ885G2305 roll-over patients)
* Documented spiking, intermittent fever (body temperature > 38°C) for at least 1 day during the screening period within 1 week before first canakinumab/placebo dose (Patients rolling-over from the CACZ885A2203 or CACZ885G2305 study will not be required to have fever for study entry)
* C-reactive protein (CRP) > 30 mg/L (normal range < 10 mg/L) (Patients rolling-over from the CACZ885A2203 or CACZ885G2305 study will not be required to have a CRP > 30 mg/L)
5. Patient*s willingness to discontinue anakinra, rilonacept, tocilizumab or other experimental drug under close monitoring (Please refer to Section 5.2 - Exclusion criteria #12 for washout period.)
6. No concomitant use of second line agents such as disease-modifying and/or immunosuppressive drugs will be allowed with the exception of:
* Stable dose of methotrexate (maximum of 20 mg/ m2/ week) for at least 8 weeks prior to the screening visit, and folic/folinic acid supplementation (according to standard medical practice of the center)
* Stable dose of no more than one non-steroidal anti-inflammatory drug (NSAID) for at least 2 weeks prior to the screening visit
* Stable dose of steroid treatment * 1.0 mg/kg/day (maximum 60 mg/day for children over 60 kg) in 1-2 doses per day of oral prednisone (or equivalent) for at least 3 days prior to baseline (Day 1)
7. Negative Purified Protein Derivative (PPD) test (< 5 mm induration) or negative QuantiFERON at screening or within 1 month prior to the screening visit, according to the national guidelines. Patients with a positive PPD test (* 5 mm induration) at screening may be enrolled only if they have either a negative chest x-ray or a negative QuantiFERON test (QFT-TB G In-Tube). If the patient has a history of Bacillus Calmette-Guérin (BCG) vaccination, then a QuantiFERON test should be performed in place of a PPD test. (Not required for CACZ885G2305 roll-over patients)
8. Patients who have completed study CACZ885A2203 and flared * 6 months after their last canakinumab dose will be considered *treatment-naïve* patients and will be required to meet all inclusion/exclusion criteria of CACZ885G2301 protocol.

Exclusion criteria

1. 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 (> 5 mIU/ mL) at screening visit
2. Female patients having reached sexual maturity (e.g. Tanner stage 2 or above), i.e. being physiologically capable of becoming pregnant UNLESS they are:

* female patients whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and/or
* using an acceptable method of contraception with a failure rate (Pearl Index (PI)) < 1. Reliable contraception should be maintained throughout the study and for 2 months after study drug discontinuation.
3. History of hypersensitivity to study drug or to biologics.
4. Diagnosis of active macrophage-activation syndrome (MAS) (Ravelli, Magni-Manzoni and Pistorio 2005) within the last 6 months
5. With active or recurrent bacterial, fungal or viral infection at the time of enrollment, including patients with evidence of Human Immunodeficiency Virus (HIV) infection, Hepatitis B and Hepatitis C infection
6. Any of the risk factors for tuberculosis (TB) such as:
* History of any of the following: residence in a congregate setting (e.g. jail or prison, homeless shelter, or chronic care facility), substance abuse (e.g. injection or noninjection); health-care workers with unprotected exposure to patients who are at high risk of TB or patients with TB disease before the identification and correct airborne precautions of the patient, or
* Close contact (i.e. share the same air space in a household or other enclosed environment for a prolonged period (days or weeks, not minutes or hours)) with a person with active pulmonary TB disease within the last year
7. With underlying metabolic, renal, hepatic, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the patient and/ or places the patient at unacceptable risk for participation in an immunomodulatory therapy. In particular, clinical evidence or history of multiple sclerosis or other demyelinating diseases, or Felty*s syndrome.
8. With significant medical conditions, which in the opinion of the Investigator will exclude the patient from the study (can be discussed on a case by case basis with Novartis)
9. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
10. Clinical evidence of liver disease or liver injury as indicated by abnormal liver function tests at screening such as AST, ALT, GGT, alkaline phosphatase, or serum bilirubin (must not exceed twice the upper limit value of the normal range for age)
11. Presence of moderate to severe impaired renal function as indicated by clinically significantly abnormal creatinine (* 1.5 x upper normal limit (ULN)) or urea values or abnormal urinary constituents (e.g., albuminuria) at screening. Evidence of urinary obstruction or difficulty in voiding at screening.
12. Use of the following therapies:
* Anakinra within 24 hours prior to Baseline visit
* Rilonacept within 1 week prior to Baseline visit
* Tocilizumab within 3 weeks prior to Baseline visit
* Etanercept within 4 weeks prior to Baseline visit
* Adalimumab within 8 weeks prior to the Baseline visit
* Infliximab within 12 weeks prior to the Baseline visit
* Rituximab within 26 weeks prior to the Baseline visit
* Leflunomide within 4 weeks prior to the Baseline visit. Documentation of a completion of a full cholestyramine elimination treatment after most recent

leflunomide use will be required.
* Thalidomide within 4 weeks prior to the Baseline visit
* Cyclosporine within 4 weeks prior to the Baseline visit
* Intravenous immunoglobulin (i.v. Ig) within 8 weeks prior to the Baseline visit
* 6-Merceptopurine, azathioprine, cyclophosphamide, or chlorambucil within 12 weeks prior to the Baseline visit
* Dapsone, mycophenolate mofetil within 3 weeks prior to the Baseline visit
* Growth hormone within 4 weeks prior to the Baseline visit
* Corticosteroids (oral prednisone (or equivalent)) > 1.0 mg/kg/day (or greater than the maximum of 60 mg/day for children over 60 kg) for at least 3 days prior to the Baseline visit
* Intra-articular, peri-articular or intramuscular corticosteroid injections within 4 weeks prior to the Baseline visit
* Any other investigational biologics (with the exception of the ones mentioned above or canakinumab (previous participation in studies CACZ885A2203 or CACZ885G2305)) within 8 weeks prior to the Baseline visit
* Any other investigational drugs, other than investigational biologic treatment, within 30 days (or 3 months for investigational monoclonal antibodies) or 5 half-lives prior to the Baseline visit, whichever is longer
Wash-out period may be longer according to local requirements.
13. Live vaccinations within 3 months prior to the start of the study. Killed or inactivated vaccines may be permitted according to the investigator*s discretion.
14. Donation or loss of blood (amount depending on age and weight, 10-20% or more of volume, see Appendix 3) within 8 weeks prior to first dosing, or longer if required by local regulation.
15. Familial and social conditions rendering regular medical assessment not possible
16. History of drug or alcohol abuse within the 12 months prior to dosing

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-01-2010
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	canakinumab

Ethics review

Approved WMO Date:	09-06-2009
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-08-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-10-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-10-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-11-2009
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	10-02-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-02-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-03-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-04-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-07-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-07-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-09-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-10-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-04-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	19-04-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-07-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2008-005479-82-NL
CCMO	NL28224.041.09