A randomized, double-blind, placebo-controlled, event-driven trial of quarterly subcutaneous canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP (CANTOS study, CACZ885M2301)

Published: 29-07-2011
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Primary: to demonstrate the superiority of at least one dose of canakinumab compared to placebo in reducing the risk of recurrent major cardiovascular disease events (cardiovascular death, non-fatal MI and stroke) in a population of clinically...

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

Summary

ID

NL-OMON35757

Source
ToetsingOnline

Brief title
CANTOS

Condition

- Coronary artery disorders

Synonym
secondary prevention after myocardial infarction

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: canakinumab, myocardial infarction, prevention, type 2 diabetes

Outcome measures

Primary outcome

Occurrence of cardiovascular death, non-fatal MI and stroke.

Secondary outcome

Hospitalization for unstable angina requiring unplanned revascularizations,

all-cause mortality, new onset type 2 diabetes, adverse events.

Study description

Background summary

Atherosclerosis is a disease characterized by chronically high inflammatory state. Inflammatory mediators are intimately implicated with the cascade of events leading to atherosclerotic plaque initiation, progression and rupture. Adverse conditions such as hyperlipidemia are associated with enrichment of a pro-inflammatory subset of monocytes. Interleukins are key mediators in the chronic vascular inflammatory response in cardiovascular disease. Lack of IL-1* or ablation of IL-1 receptor has been shown to decrease severity of atherosclerosis in apoE deficient mice. Thus, antagonism of the IL-1* mediated inflammation is a primary and attractive target for ameliorating the vessel wall inflammation associated with atherosclerosis.
Canakinumab (ACZ885) is a fully human monoclonal anti-human IL-1* antibody, being developed for the treatment of IL-1* driven inflammatory diseases. It is designed to bind to human IL-1* and thus blocks the interaction of this cytokine with its receptors. The antagonism of the IL-1* mediated inflammation using canakinumab in lowering high sensitivity C-reactive protein (hs-CRP, an independent risk factor for future cardiovascular events) and other

inflammatory marker levels has shown an acute phase response in patients with Cryopyrin-Associated Periodic Syndrome (CAPS) and rheumatoid arthritis. This evidence has been replicated in patients with type 2 diabetes mellitus (T2DM). Therefore, canakinumab is expected to reduce the risk of future occurrence of major cardiovascular events in patients with recent past myocardial infarction by preventing IL-1* mediated vascular wall inflammation and endothelial dysfunction.
T2DM is also a disease that is characterized by a high inflammatory state. Pre-clinical data suggests IL-1* is of key importance in the destruction of *-cells in type 2 diabetes. IL-1* antagonism inhibits * cell death, promotes * cell proliferation, potentiates * cell glucoseinduced insulin secretion and improves insulin sensitivity. For T2DM prevention canakinumab*s primary direct action is expected to prevent the IL-1* mediated destruction of pancreatic *-cells and thus prevent or delay progression of disease, which to date is a completely unmet need
The primary purpose of this trial is to test the hypothesis that canakinumab treatment of patients with MI at least one month prior to study entry and elevated hsCRP will prevent recurrent cardiovascular events. A secondary hypothesis, that canakinumab treatment in patients with MI and pre-diabetes, will prevent new onset diabetes will also be tested.

Study objective

Primary: to demonstrate the superiority of at least one dose of canakinumab compared to placebo in reducing the risk of recurrent major cardiovascular disease events (cardiovascular death, non-fatal MI and stroke) in a population of clinically stable post-MI patients with elevated hsCRP receiving standard of care.
Secondary objectives: Endpoint of CV death, non-fatal MI, stroke, and hospitalization for unstable angina requiring unplanned revascularizations. Composite endpoint of all-cause mortality, non-fatal MI and stroke. Endpoint of all-cause mortality. New onset type 2 diabetes. Long-term safety.

Study design

Multicenter randomized double blind phase III parallel group study with placebo control. Prescreening for elevated hsCRP.
Randomisation (1:1:1:1*) to treatment with:
* Canakinumab 50 mg (s.c. injections week 1 and 3, therafter 1x/3 months)
* Canakinumab 150 mg (s.c. injections week 1 and 3, therafter 1x/3 months)
* Canakinumab 300 mg (s.c. injections week 1 and 3, therafter 1x/3 months)
* Placebo.
Event-driven study, expected duration approx. 6 years.
Independent DSMB.
2 interim analyses for efficacy: after approx. 50 and 75% of CV events are available.

Approx 17200 patients, 275 in NL
At the end of the study possibility to join an open-label follow-up study.

Intervention

Treatment with canakinumab or placebo.

Study burden and risks

Risk: Adverse effects of study medication.
Burden: Max. study duration approx. 6 years. 5 visits in 1st 3 months, therafter every 3 months. Duration 1-2 h.
Physical examination annually.
Blood tests 1st year 8x, therafter 2x/year, 20-55 ml/occasion. At screening HIV and hepatitis B-C. Optional pharmacogenetic/-genomics blood tests (3x 10 ml).
Pregnancy test (if relevant) 2x.
ECG annually.
TBC test at screening (blood), if needed chest X ray.
Monitoring for macula degeneration every 6 months.
EQ-5D questionnaire (in NL the other questionnaires will not be used) 6x in 1st year and year 3 and 4.
Life style councelling.

Contacts

Public
Novartis

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NL
Scientific
Novartis

Raapopseweg 1
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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Females (non-child-bearing potential or adequate contraception) and males *18 years of age.
* MI with or without ST elevation (detailed criteria see protocol) at least 30 days before randomization.
* hsCRP * 2 mg/L at prescreening (* 28 days after MI or PCI).

Exclusion criteria

* Pregnancy, breast feading.
* Planned CABG or PCI.
* Major non-cardiac surgical or endoscopic procedure within past 6 months.
* Multi-vessel CABG surgery within the past 3 years.
* Symptomatic patients with Class IV heart failure.
* Uncontrolled hypertension.
* Uncontrolled diabetes.
* Prior malignancy other than basal cell skin carcinoma.
* History, evidence of or risk factors for active TB infection (see protocol for details).
* History of ongoing, chronic or recurrent infectious disease.
* Patients with suspected or proven immunocompromised state.
* Live vaccinations within 3 months prior to the randomization visit or live vaccinations planned during the trial.
* Any biologic drugs targeting the immune system.
* Any life threatening condition with life expectancy < 5 years, other then vascular disease.

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:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-09-2011
Enrollment:	260
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ilaris
Generic name:	canakinumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	29-07-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-10-2011

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-12-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-01-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-01-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-03-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-06-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-01-2013

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2015

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-01-2017

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
Other	clinicaltrials.gov, registratienummer n.n.b.
EudraCT	EUCTR2010-022970-14-NL
CCMO	NL36844.018.11