A randomized, double-blind, placebo controlled multiple dose study of subcutaneous ACZ885 for the treatment of abdominal aortic aneurysm

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To assess the effect of ACZ885 on AAA size and growth rate as measured with ultrasound at 12 months.Secondary Objectives * To assess the safety and tolerability of monthly 150 mg subcutaneousdoses of ACZ885 in subjects with AAA over a treatment...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Aneurysms and artery dissections
Study type	Interventional

Summary

ID

NL-OMON38947

Source
ToetsingOnline

Brief title
Phase II study for the treatment of abdominal aortic aneurysm

Condition

- Aneurysms and artery dissections

Synonym
Abdominal aortic aneurysm; dilation of the aorta in the abdomen

Research involving
Human

Sponsors and support

Primary sponsor: Novartis

Source(s) of monetary or material Support: Novartis Pharma Services AG

Intervention

Keyword: AAA, Abdominal Aortic Aneurysm, Abdominal Ultrasound, IL-1

Outcome measures

Primary outcome

Primary efficacy variables will be the AAA size and growth rate (change from

baseline AAA size per year) from the ultrasound assessment.

Secondary outcome

Volumetric and biophysical profiling data from CT scan of AAA, as well as

hs-CRP, IL-6, total IL-1* and immunoglobulins.

The number and percentage of subjects with major cardiovascular events (MACE),

acute or

elective aneurysm repair, aneurysm rupture, death (any cause) and any other

clinical events of

special interest over the 12-month treatment period.

Safety parameters: all vital signs data, ECG data, laboratory data, adverse

events and immunogenicity data.

Study description

Background summary

Abdominal aortic aneurysm (AAA) is a condition characterized by abnormal dilation of the abdominal aorta. As the AAA grows, the risk of aortic rupture and death also grows. AAA affects ~3.5 million individuals in the USA alone, resulting in ~55,000 deaths annually in the USA and EU. The incidence of AAA is expected to increase with the world*s aging population, and it remains vastly undertreated. Current clinical management of AAA relies on appropriately timed

endovascular stent graft procedures or open surgery, usually triggered by a critical AAA size. Assessing aneurysm size and growth rate are the foundations for clinical decision making at this time, since both are associated with AAA rupture rate. While surgical intervention for AAA remains the standard of care and new technologies such as endovascular stent grafts appear promising, these options are not without detriment. Surgical mortality is high (~5% open repair, up to 1.7% endovascular), late complications are frequent (25-40% for endovascular), and procedures are costly. The pathophysiology of AAA involves three main processes: inflammation, proteolysis, and apoptosis. Substantial evidence suggests that the IL-1* protein plays a role in each of these processes. Preclinical data data support a hypothesis that IL-1* is important in AAA pathogenesis. In AAA patients, inhibition of systemic IL-1* should decrease inflammation, reduce proteolysis, and diminish smooth muscle cell apoptosis. These effects should, in turn, structurally stabilize the aneurysm and ultimately slow or halt its growth. If clinically meaningful effects are observed, ACZ885 therapy in AAA may delay or obviate the need for risky and expensive procedures and surgeries. At the present time, there are no efficacy or safety studies in humans with AAA for any anit-IL-1* therapies.

Study objective

To assess the effect of ACZ885 on AAA size and growth rate as measured with ultrasound at 12 months.
Secondary Objectives * To assess the safety and tolerability of monthly 150 mg subcutaneous
doses of ACZ885 in subjects with AAA over a treatment period of 12months.

Study design

This is a non-confirmatory, double-blind, randomized, placebo-controlled, two-arm parallel group study in subjects who have been diagnosed with AAA. Eligible subjects will receive 12 monthly doses of 150mg of ACZ885 or placebo administered subcutaneously as randomized in a 1:1 ratio. The size of the AAA will be followed using ultrasonography over the course of the study. The study will consist of an up to 30-day screening period, a 12-month treatment period, and an End of Study evaluation approximately 1 month after the last study drug administration.

Intervention

Monthly subcutaneous doses of 150 mg ACZ885
Monthly subcutaneous doses of placebo to 150 mg ACZ885

Study burden and risks

Before starting the study, patients will have a screening visit and will be

asked about their health and your medical history and concomitant medication. They will be physically examined and vital signs will be measured. Patients will have an ECG and blood and urine will be taken for laboratory testing. Females will have a pregnancy test. An ultrasound will also be performed. Tests will also be done for illegal *street* drugs, for HIV/AIDS, hepatitis B and C, and tuberculosis but the results of these tests will not be captured in the study database. If patients test positive for any of these tests, they will not be allowed to enroll in the study.
Patients that join the study will be asked to come to the study site approximately 14 times over about 14 months. Each visit should take about 2-3 hours.
Patients will be administered the study medicine once a month for 12 months. During the site visits, they will be clinically examined and vital signs will be measured. The patients* ongoing smoking status will also be discussed and recorded. Blood samples will be taken pre-dose at each visit. Patients will have monthly urine tests for pregnancy, if appropriate. There will be a total of 5 ultrasounds during the study: during the screening period, after 3, 6, 9 and 12 months of treatment. The ultrasounds after 3 and 9 months of treatment are for safety purposes only. At visits on months 1, 2, 3, 4, 5, 6, 9, and 12, patients will have an ECG.
For every visit, patients should fast overnight for at least 10 hours. For overnight fasts, no food or fluids are permitted (except water). Patients should take their medications as per their regular schedule for all visits, including fasted visits.
Patients will be asked to give some blood, which can make them feel faint or sick. It can also be uncomfortable and cause local bruising. All blood samples will be taken by direct needle stick. Rarely, a small blood clot may form or infection could occur at the site where the blood was taken. Blood will be taken 15 times during the study and approximately 610 mL (about 2 and a half cups) of blood will be collected in total over the 14 months of the study.
When patients are given a dose of ACZ885 or placebo this will be injected just under the surface of the skin. This may cause some reddening of the skin, itching, swelling or pain. Identified risks with ACZ885 (canakinumab) and other IL-1 receptor blockers include an increased risk of infections, injection site reactions, decreased white blood cell and platelet count, increases in ALT or AST, immunogenicity, and vertigo. Predominantly upper respiratory tract infections have been reported in subjects treated with canakinumab. Theoretical risks of ACZ885 include reduced wound healing and reduced response to vaccines.
As a result of the ECG, the skin may become a little itchy and red where the sticky pads are placed.
Ultrasound imaging (sonography) uses high-frequency sound waves to view soft tissues and does not involve ionizing radiation. There are no known adverse safety risks but ultrasound use does produce slight bioeffects on the body as the tissue heats slightly when the acoustic waves enter the body and can also produce small pockets of gas in tissue. A hand-held transducer is placed on the skin to produce the image and its application will be limited to the region of

interest (abdomen for AAA) to minimize any discomfort and risk of cavitation.

Contacts

Public
Novartis

Novartis Campus - Forum 1
Basel 4056
CH
Scientific
Novartis

Novartis Campus - Forum 1
Basel 4056
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Male and female subjects age *45 years of age
* Infrarenal abdominal aortic aneurysm with maximum diameter:
* for men *40mm and *50mm
* for women *38mm and *48mm
* On a stable medical regimen for at least 2 weeks prior to dosing
* Have an evaluable ultrasound image at screening for thequantitative determination of the AAA size
* At screening and pre-dose on Day 1, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position after the subject has rested for at least

three minutes.
Sitting vital signs should be within the following ranges:
oral body temperature between 35.0-37.5°C
systolic blood pressure, 90-170 mm Hg
diastolic blood pressure, 50-100 mm Hg
pulse rate, 40 - 100 bpm

Exclusion criteria

*Known diabetes by medical history, a HbA1c of *6.5% at screening, or on an active diabetic medical regimen
* Women of child bearing potential unless using effective methods of contraception
* Subjects on the following medications:
1) Chronic systemic steroid treatment or other systemic immunosuppression. Use oftopical, ophthalmic or inhaled steroids at doses not considered to have systemic effects is allowed. Temporary use of steroids (e.g., for asthma exacerbations) are allowed if last steroid use is more than 1 month prior to screening and the anticipated frequency of requiring such steroids are less than once per year.
2) Any biologic drugs targeting the immune system, e.g., TNF blockers, anakinra, rituximab, abatacept, tocilizumab. Any previous history of the use of such biologics is also an excluded.
* Presence of a non-healing wound or infection, including active urinary tract infections, or any recent process requiring significant tissue healing per investigator assessment. Other active infections
within 2 weeks will be excluded.
* Previous infra-renal aortic surgery
* Known aortic dissection
* Subjects should exhibit no signs of clinically concerning unstable acceleration of AAA size or growth rate at the time of enrollment per investigator assessment

Study design

Design

Study phase:	2
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):	27-02-2014
Enrollment:	24
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:	16-10-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	23-12-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	06-01-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	10-01-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	11-09-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-01-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-10-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2013-002088-25-NL
CCMO	NL46059.060.13

Study results

Date completed: 14-10-2015

Actual enrolment: 7

Summary results
Trial is onging in other countries