Evaluation of the subcutaneous administration of 30 mg of S78989 versus placebo and evaluation of the subcutaneous administration of 60mg of S78989 versus placebo, on the reduction of arterial wall inflammation in patients with marked atherosclerotic plaque inflammation.
A 28-weeks, randomized, double-blind, parallel-group, placebo controlled, international multicenter exploratory pilot study.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Interventional

Summary

ID

NL-OMON39440

Source
ToetsingOnline

Brief title
S78989-009

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
arterial wall inflammation, artherosclerosis

Research involving
Human

Sponsors and support

Primary sponsor: I.R.I.S
Source(s) of monetary or material Support: IRIS (Institut de Recherche Internationales Servier)

Intervention

Keyword: atherosclerosis, inflammation, S78989

Outcome measures

Primary outcome

The changes from baseline mean of the maximum TBR, average mean TBR, mean of

max TBR and maximum max TBR assessed by 18F-FDG PET/CT.

Secondary outcome

Efficacy/secondary endpoints

-The changes from baseline of the High-Sensitivity C-reactive protein (hs-CRP)

and interleukin 6 (IL-6) plasma concentrations,

-The changes from baseline of other markers: plasma concentrations of cytokines

IL-1*, IL-8, IL-17 and IL1-Ra.

-The changes from baseline in monocytes count.

-Safety parameters:

Physical examination including weight, systolic blood pressure and diastolic

blood pressure,

12-lead Electrocardiogram (ECG): Heart Rate, PR and RR interval, QRS duration,

and QT interval (corrected and uncorrected), and other ECG abnormalities,

Blood clinical laboratory parameters (haematology and biochemistry including

white blood cells count, creatinine clearance and LDL cholesterol),

Adverse events

-Other measurements:

Pharmacokinetic measurements

Anti-drug antibodies (ADA)

-Metabolic profiling

Optional pharmacogenomics assessement (separate informed consent form)

Study description

Background summary

Despite many therapeutic improvements, atherosclerosis remains a leading cause of mortality in developed countries and its prevalence is increasing in developing ones.
Within the cytokines, IL-1* has been shown to be present in human atherosclerotic lesions where it may contribute to vascular pathogenesis by induction of adhesion molecules, chemokines and procoagulant activity.
Gevokizumab (S 78989) is a recombinant Human Engineered* monoclonal antibody (mAb) that binds human IL-1* and regulates the activation of IL-1 receptors.
Administration of gevokizumab to patients suffering from IL-1*-mediated systemic inflammatory diseases is expected to produce rapid and sustained reductions in symptoms.
To date, the clinical experience with gevokizumab includes over 500 subjects who have been exposed to gevokizumab in a variety of clinical settings, primarily type 2 diabetes, but also type 1 diabetes, Behçet disease uveitis, rheumatoid arthritis, and acne vulgaris.

Following the availability of new preclinical and clinical data, as well as tolerance data, it was decided to evaluate an additional group of 45 patients using a higher dose of 60mg gevokuzimab (part B of same study).

Study objective

The objective of this study is to evaluate the effect of the 4 successive monthly subcutaneous administrations of 30 mg of gevokizumab (in part A) , as well as 60mg (in part B) of the protocol, versus placebo on the reduction of arterial wall inflammation in adult patients with marked arterial wall inflammation following a recent acute coronary syndrome.

Study design

This study is a phase II, randomised (2:1), double-blind, parallel-group, placebo controlled, international, multicentre, pilot, exploratory study,
The study will be performed in 45 patients (30 patients are receiving gevokuzimab, and 15 placebo), in each part of the study (A and B), with a total of 90 patients for the whole study. Gevokuzimab 30mg or 60mg will be given onze monthly, SC (4 injections in total for the study). The total duration of the study is 28 weeks, and the estimated duration of recruitment has been prolonged till 12 months. See plan in protocol Fig(8.2.1)1.
There are 7 study visits per patients: Selection (ASSE), inclusion (W000), W004, W008, W012, W016 (eind) + follow-up W028; + 2 visits for the PET-CT scan.

Intervention

placebo or gevokizumab

Study burden and risks

Risks: All drugs can cause side effects. Until now gevokizumab has been well tolerated.
As any therapy targeting IL-1*, gevokizumab may increase the risk of infections.Though it has not been observed with gevokizumab so far, there is a possibility of developing allergic reactions because of the nature of this new drug. Fever, chills and rigors, typically occurring within the first two hours following infusion, characterize these reactions. Other symptoms sometimes associated with infusion reactions include nausea, vomiting, rash, pruritus, bronchospasm (difficulty of breathing), angioedema, hypotension, hypertension, and cardiac arrhythmias. In general, most injection reactions are manageable and mild to moderate in severity, but the possibility of life-threatening reactions cannot be excluded, even if never observed with gevokizumab.

Burden:

There are 9 visits, with a probable total time investment of 17 -19 hours. The total duration of the study is 28 weeks.
There are 4 subcutaneous injections with studymedication (1ml/ time) (1 injection per month).
Physical examination: 7 times
ECG: 7 times
Bloodsampling: 5 times(ca 40 ml/ sampling time)
FDG PET-CT scan: 2 times
Optional pharmacogenomic analysis: 3 times (no extra bloodsampling) (ca 10ml/sampling time)

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Main selection criteria:
* Male or female of non-childbearing potential (contraception allowed), aged over 50 years with a documented recent (3-12 months) acute coronary syndrome (ACS) defined as the association of a chest pain episode or its equivalent and either:
o elevated troponin
o Percutaneous Coronary Intervention (PCI) performed because of the related ACS event
o significant coronary stenosis (visual assessment before any percutaneous dilatation) diagnosed in at least one native vessel on a coronary angiography performed after the event.
* Informed consent signed
* All revascularization procedures planned after the acute event, completed at least 3 months before selection visit
* Use of statins since at least 3 months before selection, and no change in use of any antidyslipidemic treatment within the 2 months prior to selection en between selection and inclusion.
Main inclusion criteria
* Patients with a maximum mean Target to Background Ratio (TBR), measured by 18-FDG PET/CT in any region of interest (left carotid, right carotid, thoracic aorta) > 1.8 at selection visit.

Exclusion criteria

Main-non selection/non-inclusion
*Pregnancy
*Type I diabetes or uncontrolled diabetes (HBA1c>9.5%),
*History of heart surgery (including coronary artery bypass graft surgery) within 1 year prior to selection,
*Chronic inflammatory diseases,
*History or symptoms of demyelinating disease
*History of malignancy within 3 years other than carcinoma in situ of the cervix, or adequately treated, non-metastatic squamous or basal cell carcinoma of the skin,
*Recent or active infectious diseases,
*Chronic infectious diseases including active tuberculosis, HIV and hepatitis B or C,
*Known immunodeficiency,
*Use of:
-Corticosteroids (>20mg/day of prednisolone or equivalent within 1 month previous selection)
-Biologic or immunosuppressive therapy within 3 months previous selection
-Live vaccine within 3 months prior to selection (with the exception of live seasonal flu and live HN1 vaccins that are permitted until 2 weeks before inclusion).

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):	14-01-2013
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Gevokizumab
Generic name:	Gevokizumab

Ethics review

Approved WMO Date:	02-11-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	12-11-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	21-03-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2013
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
EudraCT	EUCTR2012-002677-53-NL
CCMO	NL41339.018.12