A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effect of Alirocumab (SAR236553/REGN727) on the Occurrence of Cardiovascular Events in Patients Who Have Recently Experienced an Acute Coronary Syndrome

Published: 05-02-2013
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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON45085

Source
ToetsingOnline

Brief title
Odyssey Outcomes

Condition

- Coronary artery disorders

Synonym
Cardiovascular events - Acute Coronary Syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi BV
Source(s) of monetary or material Support: sanofi-aventis

Intervention

Keyword: Acute Coronary Syndrome

Outcome measures

Primary outcome

Primary endpoint

* Time from randomization to first occurrence of one of the following

Clinical Events, as determined by the CEC:

- CHD death.

- Any non-fatal MI.

- Fatal and non-fatal ischemic stroke.

- Unstable angina requiring hospitalization.

Secondary outcome

Main Secondary Efficacy Endpoint(s):

* Time from randomization to first occurrence of any CHD event (major

CHD event, unstable angina requiring hospitalization, hospitalization for

unanticipated coronary revascularization procedure).

* Time from randomization to first occurrence of any major CHD event

(CHD death, non-fatal MI).

* Time from randomization to first occurrence of any CV event defined as

follows: any non-fatal CHD event, any CV death, and non-fatal ischemic

stroke.

* Time from randomization to first occurrence of all cause mortality, nonfatal

MI, non-fatal ischemic stroke.

* Time from randomization to death (all cause mortality).

Other Secondary Efficacy Endpoint(s):

* Components of the primary end point considered individually: CHD death,

or non-fatal MI, or fatal and non-fatal ischemic stroke, unstable angina

requiring hospitalization.

* Hospitalization for unanticipated coronary revascularization procedure.

* Congestive heart failure requiring hospitalization.

Safety Endpoint(s):

* Safety endpoints: all adverse events, heart rate and blood pressure,

hematology and biochemistry assessments.

Other Endpoint(s):

* Anti-SAR236553 antibodies assessed throughout the study.

* The percent change in calculated LDL-C, in ApoB and non HDL-C.

Study description

Background summary

Patients with recent acute coronary syndrome (ACS) are at very high risk for suffering recurrent coronary events in the near term. Both epidemiological and

pharmacological intervention trials have demonstrated a strong and linear relationship between the levels of low-density lipoprotein cholesterol (LDL-C) and cardiovascular (CV) events.
SAR236553 is a fully human monoclonal antibody (mAb) directed against PCSK9.Recent studies indicate that PCSK9 binds directly to LDLR and promotes LDLR internalization and degradation.
Blocking of PCSK9 thus increases the activity of the LDLR, and with that the clearing of LDL cholesterol from the blood.
SAR236553 binds with moderate to high affinity to human, monkey, rat, mouse and hamster PCSK9. In vivo studies in animal models and human genetic studies suggest that inhibition of PCSK9 binding to LDLR by SAR236553 is anticipated to be an effective method of lowering
LDL-C, by increasing the number of LDLR, thus increasing the removal of LDL/LDL-C from circulation. Consequently SAR236553 is expected to reduce the risk of cardiovascular disease.

Study objective

Primary objective
The primary objective of this study is to compare the effect of alirocumab with placebo on the occurrence of cardiovascular events (composite endpoint of coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization) in patients who have experienced an acute coronary syndrome (ACS) event 4 to 52 weeks prior to randomization and are treated with an LMT regimen that is statin-intensive (defined as atorvastatin 40 or 80 mg, or rosuvastatin 20 or 40 mg) or at maximally tolerated dose of these given statins and optimized for long-term chronic use with other non-statin LMT(s) at investigator*s discretion.

Secondary objective(s)
To compare the efficacy of alirocumab versus placebo on secondary endpoints (any CHD event, major CHD event, any CV event, composite of all-cause mortality/non-fatal MI/non-fatal ischemic stroke, all-cause mortality).
A Clinical Events Committee (CEC) will be established to adjudicate, in a blinded fashion, events corresponding to the primary and secondary cardiovascular endpoints as well as all causes of death.
* To evaluate the safety and tolerability of alirocumab throughout the study.
* To evaluate the development of anti- alirocumab antibodies.
* To evaluate the effect of alirocumab on low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), and non-highdensity lipoprotein cholesterol (non-HDL-C).

Study design

This is a double-blind, randomized, placebo-controlled, parallel-group study, multi-national, multicenter study. Phase III

Intervention

Treatment with SAR236553 or placebo

Study burden and risks

Side effects of the study medication. The most common side effects reported in previous completed studies of SAR236553 in patients who received at least one dose include: injection site reactions, dizziness, headache, nausea and diarrhea.
Duting the study, the LDL cholesterol levels may go to low levels; lower than what is usually seen with other medicines used to treat high cholesterol. The potential consequences of developing low LDL cholesterol are unknown.
In studies done in rats, findings were seen in the eyes of some animals. In a 6-month study, the finding was in the nerve of the eye. In most cases, this was thought to be caused by trauma to the eye that was the result of a study procedure. The meaning of this finding is not clear. In studies done in people treated for up to 12 weeks with SAR236553, no changes in vision were reported.
Other potential risks that have been linked to blocking PCSK9: a decrease in the immune defense, liver disease, colorectal cancer or increased susceptibility to hepatitis C virus infection; however, it should be noted that these potential risks have not been identified in animal studies conducted in rats and monkeys for up to 6 months with SAR236553 or in prior and ongoing human studies for up to 12 weeks with SAR236553.
During blood draws, there may be pain and/or bruising where blood is taken. Blood clots may form and infections may occur, but these events are rare.
A small number of patients were noted to have experienced allergic reaction associated with administration of the study drug.
The estimated study duration in 64 months. A total of visits to the institution must be made. For some, the patient must have fasted for at least 8 hours. On 8 visits, the patient will have to undergo a physical examination. During the course of the study, the patient is asked to maintain a diary, which will be reviewed on 16 visits. Also, an EQ-5D questionnaire will be administered on 15 visits. On 2 occasions there will be an ECG measurement. Also, they have to self inject the study drug every 2 weeks (1ml SC injection)

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

Hospitalization for ACS (ST-elevation MI, non-ST elevation MI or high-risk unstable angina) defined by:
- Ischemic symptoms with unstable pattern, occurring at rest or minimal exertion within 72 hrs of an unscheduled hospital admission, due to presumed or proven obstructive coronary disease AND at least one of the following:
o Elevated cardiac biomarkers, OR
o Resting ECG changes consistent with ischemia or infarction AND additional evidence of obstructive coronary disease;Patient lipid levels not adequately controlled at V2 (qualifying visit), despite evidence-based lipid lowering therapy (including intensive atorvastatin/rosuvastatin therapy or maximally tolerated dose of either of these 2 statins), or other non-statin LMTs. Inadequate lipid control means that patient must meet at least one of the following criteria at V2 to qualify:
- LDL-C * 70 mg/dL (*1.81 mmol/L), or
- ApoB * 80 mg/dL (* 0.8 g/L), or
non-HDL-C * 100 mg/dL (*2.59 mmol/L)

Exclusion criteria

All of the 3 following criteria are concomitantly present at the qualifying visit (V2):
- LDL-C <70 mg/dL (<1.81 mmol/L), and
- ApoB < 80 mg/dL (< 0.8 g/L), and
- non-HDL-C <100 mg/dL (<2.59 mmol/L)
NOTE: If not all 3 but only 1 or 2 criteria are present then the patient may qualify.
* Age < 40 years
* Patients in whom the qualifying index ACS event occurred less than 4 weeks (28 days) or more than 52 weeks (+ 5 days) prior to randomization visit (V3)
* Not on stable LMT doses (statin and/or non-statin LMT) for at least 2 weeks prior to qualifying visit (V2)
* Uncontrolled hypertension (multiple readings with SBP > 180 mmHg or DBP > 110 mmHg) at V3
* New York Heart Association Class III or IV congestive heart failure persisting despite treatment or if measured LVEF <25%
* Known history of hemorrhagic stroke
* Fasting serum triglycerides (TG) >400 mg/dL (>4.52 mmol/L) prior to randomization
* New ACS event occurring within 2 weeks prior to the randomization Visit (V3);Coronary revascularization (PCI or CABG) planned after randomization and/or performed within 2 weeks prior to the randomization Visit (V3)

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):	15-07-2013

Enrollment:	743
Type:	Actual

Ethics review

Approved WMO Date:	05-02-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-05-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-07-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-10-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-10-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-11-2013

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-11-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-02-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-06-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	06-06-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-07-2014
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:	30-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-12-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-01-2015
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:	09-02-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-05-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-05-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-11-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-12-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-01-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-01-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	03-06-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-07-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-08-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-06-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-10-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-11-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-12-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	22-01-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-06-2018
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	EUCTR2011-005698-21-NL
ClinicalTrials.gov	NCT01663402
CCMO	NL42275.060.13