A Double-blind, Randomized, Placebo-controlled, Multicenter Study Assessing the Impact of Additional LDL-Cholesterol Reduction on Major Cardiovascular Events When Evolocumab (AMG 145) is Used in Combination With Statin Therapy In Patients with Clinically Evident Cardiovascular Disease

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Primary Objective: To evaluate the effect of treatment with AMG 145, compared with placebo, on the risk for cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization, whichever occurs...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON53167

Source
ToetsingOnline

Brief title
AMG145-20110118 FOURIER

Condition

- Cardiac disorders, signs and symptoms NEC
- Metabolism disorders NEC

Synonym
dyslipidemia, elevated cholesterol

Research involving
Human

Sponsors and support

Primary sponsor: Amgen
Source(s) of monetary or material Support: Amgen

Intervention

Keyword: AMG145, cardiovascular disease, dyslipidemia, placebo

Outcome measures

Primary outcome

Time to cardiovascular death, myocardial infarction, hospitalization for

unstable angina, non-hemorrhagic stroke, or coronary revascularization,

whichever occurs first.

Secondary outcome

- Time to cardiovascular death, myocardial infarction, or non-hemorrhagic

stroke, whichever occurs first

- Time to death by any cause

- Time to first hospitalization for worsening heart failure

Study description

Background summary

AMG 145 is a fully human monoclonal immunoglobulin (Ig) G2 that binds specifically to human proprotein convertase subtilisin/kexin type 9 (PCSK9) and prevents the interaction of PCSK9 with the LDL receptor. AMG 145 caused a dose related inhibition of PCSK9 binding to the LDL receptor and of the PCSK9-mediated reduction in low-density lipoprotein (LDL) uptake in hepatic

cells. Treatment of cells with a combination of AMG 145 and statin increased LDL receptor protein levels more than treatment with either alone. Single administrations in humans produced decreases in mean
LDL-C with subsequent returns to baseline. Across the dose groups, the decreases were dose-related. Overall, AMG 145 appeared to be well tolerated at the IV and SC doses administered in this FIH study. Incidences of overall adverse events and treatment-related adverse events did not differ notably between treatment groups.

The present study is designed to assess the effects on the risk of cardiovascular events of SC administration of AMG 145 every 2 and every 4 weeks, compared to placebo, in patients with clinically evident cardiovascular disease.

Study objective

Primary Objective: To evaluate the effect of treatment with AMG 145, compared with placebo, on the risk for cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization, whichever occurs first, in subjects with clinically evident
cardiovascular disease.

Secondary Objectives:
To evaluate the effect of treatment with AMG 145, compared with placebo, in subjects with clinically evident cardiovascular disease on the risk for:
- cardiovascular death, myocardial infarction, or stroke
- death by any cause
- hospital admissions for worsening heart failure

Study design

Phase 3, multicenter, double-blind, randomized, placebo controlled, parallel group, endpoint driven
Background therapy is atorvastatin, uptitrated to a maximum stable dose of 80 mg.
Randomisation (1:1):
- AMG145 (Q2W or Q4W, subject is allowed to choose which during the study)
- placebo (Q2W or Q4W, subject is allowed choose which during the study)

Screeningperiod of max 12 weeks. Treatment period max 56 months.
Independent DSMB
App 27500 subjects
The study will end when at least 1630 subjects have experienced a secondary endpoint event of cardiovascular death, myocardial infarction, or stroke.

Intervention

Treatment with AMG 145 or placebo (every two weeks or four weeks).

Study burden and risks

Risks: Side effects of study medication.
Burden: Maximum duration up to 5 years, up to 24 visits. Max 16 visits fasting.
Duration screen visit about 2-3 hours. Further visits max 1 hour.
3 SC injections of 2 ml (placebo) during screening.
Every 2 weeks 1 SC injection of 2 ml or every 4 weeks 3 SC injections of 2 ml, for up to five years.
Physical examination 2x.
Blood test 15 x max, 20-30 mL at a time, extra blood if subject has an increased risk of hepatitis C (max 72,5 ml extra)
Pregnancy test (if relevant) max 12 times (at screening, randomization and then every 24 weeks)
Urinalysis max 6 x (at screening and every 48 weeks)
EKG 2x
Dietary counseling.

Contacts

Public
Amgen

Minervum 7061
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NL
Scientific
Amgen

Minervum 7061
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NL

Trial sites

Listed location countries

Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, India, Ireland, Israel, Italy, Japan, Korea (the Republic of), Latvia, Lithuania, Malaysia, Mexico, Netherlands , New Zealand, Norway, Philippines , Poland, Portugal, Romania, Russian Federation , Slovakia,

South Africa, Spain, Sweden, Switzerland, Taiwan (Province of China), Turkey, Ukraine, United Kingdom, United States of America

Eligibility criteria

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

Inclusion criteria

* 40 to * 85 years of age
history of clinically evident cardiovascular disease as signified by a recent (within 5 years) myocardial infarction or non-hemorrhagic strokeor symptomatic PAD (intermittent claudication with ankle-brachial index [ABI] < 0.85, or peripheral arterial revascularization procedure or amputation due to atherosclerotic disease);
either history of type 2 diabetes or, if not diabetic, one of the following: age * 65 years at randomization (and *85 at time of informed consent) the index event within 6 months of screening, an additional prior MI or non non-hemorrhagic stroke, current daily cigarette smokinghistory of symptomatic peripheral vascular disease, or * 2 additional risk factors, as detailed in the study protocol.
In addition, after * 4 weeks of a stable lipid stabilisation therapy, LDL-C must be * 70 mg/dL (* 1.8 mmol/L) or non HDL-C must be * 100 mg/dL (> 2.6
mg/dL). Fasting triglycerides must be * 400 mg/dL (4.5 mmol/L).

Exclusion criteria

New York Heart Failure Association (NYHA) class III or IV or last known left ventricular ejection fraction < 30%;
uncontrolled or recurrent ventricular tachycardia systolic blood pressure (SBP) > 180 mmHg or diastolic BP (DBP) > 110 mmHg;
thyroid stimulating hormone < 1.0 time lower limit of normal (LLN) or >1.5 times upper limit of normal (ULN),
estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73m2, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2x ULN, creatine kinase (CK) > 5x ULN
recipient of any major organ transplant (eg, lung, liver, heart, bone marrow);
personal or family history of hereditary muscular disorders
severe, concomitant non-cardiovascular disease that is expected to reduce life expectancy to less than 3 years
known history of hemorrhagic stroke;
major active infection, or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction;
use of cholesterylester transfer protein (CETP) inhibition treatment within 12 months prior to

randomization;
prior use of PCSK9 inhibition treatment other than AMG 145.
The following lipid-lowering therapies are excluded for 6 weeks prior to screening and during the duration of the
study: prescription lipid-regulating drugs other than statins and ezetimibe (eg, bile-acid sequestering resins,
fibrates and derivatives), niacin (> 200 mg QD), and red yeast rice.
Pregnancy, inadequate contraception, breast feeding

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):	21-05-2013
Enrollment:	998
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Evolocumab (AMG 145)
Generic name:	Evolocumab (AMG 145)
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	placebo

Generic name:	placebo

Ethics review

Approved WMO Date:	15-11-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-01-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-03-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-03-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-04-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-10-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-10-2013
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-01-2014
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:	12-05-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-08-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-11-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-12-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-06-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	17-09-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-12-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-12-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-04-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-10-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-10-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-11-2016
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	2012-001398-97
ClinicalTrials.gov	NCT01764633
CCMO	NL40997.060.12