A Double-blind, Randomized, Multicenter Study to Evaluate Safety and Efficacy of AMG 145, Compared With Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor (AMG 145 20110116)

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Primary: To evaluate the effect of 12 weeks of subcutaneous (SC) AMG 145 every-2-weeks (Q2W) and every-4-weeks (Q4W), compared with ezetimibe, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C).Secondary objectives:...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metabolism disorders NEC
Study type	Interventional

Summary

ID

NL-OMON37175

Source
ToetsingOnline

Brief title
AMG20110116

Condition

- Metabolism disorders NEC

Synonym
hypercholesterolemia; elevate cholesterol

Research involving

Human

Sponsors and support

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

Intervention

Keyword: AMG 145, Ezetimibe, Hypercholesterolemia, Statin intolerance

Outcome measures

Primary outcome

Percent change from baseline in LDL-C at week 12.

Secondary outcome

Adverse events, Absolute change from baseline in LDL-C at week 12, Percent change from baseline at week 12 in: non-HDL-C, ApoB total cholesterol/HDL-C ratio ApoB/ApoA1 ratio, Lp(a), triglyceriden, HDL-C.

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 evaluate the effects of a subcutaneous AMG 145 every 2 and every 4 weeks, compared with ezetimibe in subjects with

hypercholesterolemia who do not tolerate the required statin dose needed to reduce LDL-C to the target level.

Study objective

Primary: To evaluate the effect of 12 weeks of subcutaneous (SC) AMG 145 every-2-weeks (Q2W) and every-4-weeks (Q4W), compared with ezetimibe, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C).
Secondary objectives: Safety and tolerability. Other lipid parameters.

Study design

Multicenter randomized double-blind phase III parallel-group placebo-controlled study.
Randomization (2:2:1:1) to:
* AMG 145 140 mg (s.c. injections every 2 weeks)
* AMG 145 420 mg (s.c. injections every 4 weeks)
* Ezetimibe 10 mg daily (plus placebo to AMG 145 every 2 weeks).
* Ezetimibe 10 mg daily (plus placebo to AMG 145 every 4 weeks).
Screening period of max. 6 weeks. Treatment period 12-14 weeks.
Statin use: none or low dose.
Stratification according to LDL-C value at screening and any ezetimibe use.
Independent DSMB.
Approx. 300 patients.

Intervention

Treatment with AMG 145 (every 2 or 4 weeks) or ezetimibe.

Study burden and risks

Risk: Adverse effects of study medication.
Burden: Max. study duration approx. 20 weeks. 6-8 visits; 6 visits fasting.
Duration 2 h.
3 SC injections (2 ml each) with placebo during screening period.
Physical examination 2x.
Blood tests 6x, 20-30 ml/occasion.
Samples for biomarker development (60 ml).
Optional pharmacogenetic/-genomics blood tests.
Optional extra PK blood sampling (3 extra visits, 1 sample to 5 ml/occasion).
Pregnancy test (if relevant) 5x.
Urine tests 2x.
ECG 4x.
Dietary counseling.

Contacts

Public
Amgen BV

Minervum 7061
Breda 4817 ZK
NL
Scientific
Amgen BV

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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 18-80 (inclusive) years of age.
* Currently no statin or low-dose statin (see protocol page 44 for details).
* Fasting LDL-C at screening:
a) * 2.6 mmol/L with diagnosed CHD or are CHD risk equivalent or
b) * 3.4 mmol/L without diagnosed CHD or risk equivalent and 2 or more risk factors or
c) * 4.1 mmol/L without diagnosed CHD or risk equivalent and with 1 or no risk factors
* Statin intolerance (see protocol page 44 for details).
* Stable lipid lowering therapy prior to LDL-C screening for * 4 weeks if currently on a statin and/or bile-acid sequestering resin and/or stanol; ezetimibe must be discontinued for * 4 weeks before LDL-C screening.
* Fasting triglycerides * 4.5 mmol/L.

Exclusion criteria

* NYHA III or IV heart failure, or known left ventricular ejection fraction < 30%.
* Uncontrolled cardiac arrhythmia, see protocol page 45 for details.
* Myocardial infarction, unstable angina, PCI, CABG or stroke within 3 months prior to randomization.
* Planned CABG or PCI.
* Type 1 diabetes or newly diagnosed (within 6 months of randomization) type 2 diabetes, poorly controlled type 2 diabetes (HbA1c > 8.5%), newly diagnosed type 2 diabetes (within 6 months of randomization), laboratory evidence of diabetes during screening (fasting plasma glucose * 7.0 mmol/L or HbA1c * 6.5%) without prior diagnosis of diabetes.
* Uncontrolled hypertension.
* Red yeast rice, > 200 mg niacin daily or prescription lipid-regulating drugs (eg, fibrates and derivatives) other than statins, ezetimibe, bile-acid sequestering resin, stanols and stanol esters in the past 6 weeks.
* CETP inhibitor in the last 12 months.
* Active infection.
* 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:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-04-2013
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AMG 145
Generic name:	AMG 145
Product type:	Medicine
Brand name:	Ezetrol
Generic name:	ezetimibe
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	13-09-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-10-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-03-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2013
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
Other	clinicaltrials.gov; registratienummer n.n.b.
EudraCT	EUCTR2012-001364-30-NL
CCMO	NL40965.018.12