A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 on LDL-C in Subjects with Heterozygous Familial Hypercholesterolemia (study 20110117)

Published: 13-09-2012
Last updated: 26-04-2024

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

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON39059

Source
ToetsingOnline

Brief title
AMG20110117

Condition

- Metabolic and nutritional disorders congenital

Synonym
hypercholesterolemia; elevated cholesterol

Research involving

Human

Sponsors and support

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

Intervention

Keyword: AMG 145, Familial Hypercholesterolaemia, placebo

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

Familial hypercholesterolemia is a rare disease. In its heterozygous form, it affects about one in five hundred people. When is heterozygous familial hypercholesterolemia undiagnosed or untreated, the cumulative risk of CHD by the age of sixty years is more than 60% among men and more than 30% among women. Many patients with heterozygous familial hypercholesterolemia fail to reach goal even with maximal use of statins and other add on agents such as ezetimibe or niacin. There is a major unmet medical need for a much more effective add-on than ezetimibe in these patients.
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 placebo, in terms of efficacy and safety in subjects with heterozygous familial hypercholesterolemia.

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 placebo, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in subjects with heterozygous familial hypercholesterolemia.
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)
• Placebo (s.c. injections every 2 weeks).
• Placebo (s.c. injections every 4 weeks)
Screening period of max. 6 weeks. Treatment period 12-14 weeks.
Stratification according to LDL-C value at screening and any ezetimibe use.
Independent DSMB.
Approx. 300 patients.

Intervention

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

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 5x, 20-30 ml/occasion.
Samples for biomarker development (60 ml).
Optional pharmacogenetic/-genomics blood tests (no extra blood needed).

Optional extra PK blood sampling (3 extra visits, 1 sample to 5 ml/occasion).
Pregnancy test (if relevant) 6x.
Urine tests 2x.
ECG 4x.
Dietary counseling.

Contacts

Public
Amgen BV

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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.
• Heterozygous familial hypercholesterolemia by having met the diagnostic criteria outlined by the Simon Broome Register Group (Scientific Steering Committee 1991), see protocol page 35-36 for details.

• On an approved statin, with or without additional lipid-lowering treatment (see exclusion criteria as well), with stable dose(s) for at least 4 weeks before LDL-C screening.
• Fasting LDL-C >= 2,6 mmol/L by central laboratory at screening.
• Fasting triglycerides <= 4,5 mmol/L by central laboratory at screening.

Exclusion criteria

• LDL or plasma apheresis within 4 months prior to randomization.
• NYHA III or IV heart failure, or known left ventricular ejection fraction < 30%.
• Uncontrolled cardiac arrhythmia, see protocol page 36 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 3 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, omega-3 fatty acids ([eg, DHA and EPA combined] [> 1000 mg/day]) or prescription lipid-regulating drugs (eg, fibrates and derivatives) other than statins, ezetimibe, bile-acid sequestering resin, stanols, or regulatory approved and marketed niacin.
• 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:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-04-2013
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AMG 145
Generic name:	AMG 145

Ethics review

Approved WMO Date:	13-09-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-10-2012
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:	02-04-2013
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	EUCTR2012-001365-32-NL
CCMO	NL40966.018.12