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

Published: 07-07-2011
Last updated: 29-04-2024

Primary: To evaluate the effect of 12 weeks of subcutaneous (SC) AMG 145, compared with placebo, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in subjects with heterozygous familial hypercholesterolemia.Secondary...

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

Summary

ID

NL-OMON36148

Source
ToetsingOnline

Brief title
AMG20090158

Condition

- Metabolic and nutritional disorders congenital

Synonym
hypercholesterolaemia; 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 in non-HDL-C at week 12, Percent change from baseline in ApoB at week 12, Percent change from baseline in the total cholesterol/HDL-C ratio at week 12, Percent change from baseline in ApoB/ApoA1 ratio at week 12.

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 12 weeks of subcutaneous AMG 145, 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, 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. PK.

Study design

Multicenter randomized double-blind phase II parallel-group placebo-controlled study.
Randomisation (1:1:1) to:
* AMG 145 350 mg (s.c. injections every 4 weeks)
* AMG 145 420 mg (s.c. injections every 4 weeks)
* Placebo.
Screening period of max. 6 weeks. Treatment period 12 weeks.
Independent DSMB.
An interim analysis including PKPD modeling, will be performed to guide future clinical development plans. There are no plans to modify or discontinue this study based on the efficacy results of the interim analysis.
Approx. 150 patients.
After study ends, possibility to enter an open follow-up study.

Intervention

Treatment with AMG 145 or placebo.

Study burden and risks

Risk: Adverse effects of study medication.
Burden: Max. study duration approx. 18 weeks. 6 visits (fasting). Duration 2 h.
3 SC injections (6 ml).
Physical examination 2x.
Blood tests 6x, 20-40 ml/occasion.
Optional pharmacogenetic blood tests (3x 10 ml).

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

Contacts

Public
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Scientific
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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 18-75 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 for details.
* On an approved statin, with or without ezetimibe, with stable dose(s) for at least 4 weeks

before LDL-C screening.
* Fasting LDL-C * 100 mg/dL by central laboratory at screening.
* Fasting triglycerides * 400 mg/dL by central laboratory at screening.

Exclusion criteria

* LDL or plasma apheresis within 12 months prior to randomization.
* NYHA III or IV heart failure, or known left ventricular ejection fraction < 30%.
* Uncontrolled cardiac arrhythmia, see protocol 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, or poorly controlled type 2 diabetes (HbA1c > 8.5%).
* Uncontrolled hypertension.
* Active infection.
* Pregnancy, inadequate contraception, breast feeding.

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):	06-10-2011
Enrollment:	25
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	07-07-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-12-2011
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, regsitratienummer n.n.b.

Register	ID
EudraCT	EUCTR2011-001528-39-NL
CCMO	NL37058.018.11