A Double-blind, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of AMG 145, Compared With Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor Due to Muscle Related Side Effects

Published: 10-03-2014
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Primary objective:To evaluate the effect of AMG 145 administered subcutaneously (SC) once every month (QM) compared with ezetimibe (Part B), on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in hypercholesterolemic…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lipid metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON45082

Source
ToetsingOnline

Brief title
AMG145 20120332 GAUSS-3

Condition

- Lipid metabolism disorders

Synonym
hypercholesterolemia; elevate cholesterol

Research involving
Human

Sponsors and support

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

Intervention

Keyword: AMG 145, Hypercholesterolemia, PCSK-9, Statin intolerance

Outcome measures

Primary outcome

Percent change from baseline in LDL-C after 24 weeks treatment with AMG145 or ezetimibe.

Secondary outcome

Adverse events, Absolute change from baseline in LDL-C after 24 weeks of treatment, Percent change from baseline after 24 weeks of treatment in: non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, Lp(a), triglyceriden, HDL-C, VLDL-C. Percent of subjects attaining LDL-C < 70 mg/dL (1.81 mmol/L).

Study description

Background summary

There is an established unmet medical need for patients with dyslipidemia who experience muscle-related side effects when using statins.

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 design supports advice from regulatory agencies requesting a scientifically rigorous study to identify statin-intolerant patients through active statin rechallenge.

Study objective

Primary objective:
To evaluate the effect of AMG 145 administered subcutaneously (SC) once every month (QM) compared with ezetimibe (Part B), on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in hypercholesterolemic subjects who are unable to tolerate an effective dose of a statin due to muscle related side effects (MRSE).

Study design

Multicenter randomized double-blind phase III parallel-group placebo-controlled study.

Part A:
Screening period of max. 4 - 8 weeks.
Re-challenge with atorvastatin. Randomisation atorvastatin 20 mg vs placebo 1:1, with cross-over after 10 weeks.
Duration: max. 24 weeks
Number of patients: 500

Part B:
Randomisation AMG 145 420 mg vs ezetimibe 10 mg 2:1. All patients will take a daily tablet ezetimibe/placebo and receive a subcutaneous injection of AMG145/placebo every 4 weeks.
Duration: 6 months
Number of patients expected: 100

Part C:
Open-label AMG145 420 mg, subcutaneous injection every 4 weeks

Duration: 2 years
Number of patients: all patients from Part B, willing to continue in part C

Intervention

Treatment with atorvastatin/placebo (part A)
Treatment with AMG145/placebo and ezetimibe/placebo (part B)
Treatment with AMG 145 (part C)

Study burden and risks

Risk:
Adverse effects of study medication.

Burden:
See protocol page 45 - 49 ''Schedules of Assessments''.
Max. study duration approx 3 years. Max. about 25 visits (all fasting).
Duration 2 h. 3 SC injections of 1 ml (placebo) during screening.
Monthly administration of study medication: 3x1 injection of 1 ml by using auto-injectors OR 1x1 injection of 3,5 ml by using the personal injector.
Physical examination 2x. Blood tests during all visits, 20-30 ml/occasion.
Blood samples for biomarker development (116 ml in total). Pregnancy test (if relevant). Urine tests 2x. ECG 4x. Dietary counseling. Completion of questionnaires.

Contacts

Public
Amgen

Minervum 7061
Breda 4817 ZK
NL
Scientific
Amgen

Minervum 7061
Breda 4817 ZK
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
• Not at LDL-C goal
• History of statin intolerance
• Lipid lowering therapy has been stable prior to LDL-C screening for at least 4 weeks if currently on a bile-acid sequestering resin and/or stanol
• Fasting triglycerides <= 400 mg/dL (4.52 mmol/L) by central laboratory at screening

Exclusion criteria

• History of haemorrahagic stroke
• Personal or family history of hereditary muscular disorders
• NYHA III or IV heart failure, or last known LVEF < 30%
• Uncontrolled serious cardiac arrhythmia
• Myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or stroke within 3 months prior to randomization
• Planned cardiac surgery or revascularization
• Type 1 diabetes, poorly controlled type 2 diabetes (HbA1c > 8.5%), newly diagnosed type 2 diabetes, or laboratory evidence of diabetes during screening
• Uncontrolled hypertension
• Use of red yeast rice, > 200 mg/day niacin, or prescription lipid-regulating drugs (eg, fibrates and derivatives, statins or ezetimibe) other than bile-acid sequestering resin, or stanols and stanol esters
• Use of cholesterylester transfer protein (CETP) inhibitor
• Treatment in the last 3 months prior to LDL-C screening with any of the following drugs: systemic cyclosporine, systemic steroids, vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions
• Uncontrolled hypothyroidism or hyperthyroidism as defined by TSH < 1.0 time the lower limit of normal or >1.5 times the ULN, respectively, at screening.
• Moderate to severe renal dysfunction
• Active liver disease or hepatic dysfunction

• Known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction
• Diagnosis of deep vein thrombosis or pulmonary embolism within 3 months prior to randomization

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-05-2014
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AMG145
Generic name:	AMG145
Product type:	Medicine
Brand name:	Ezetrol
Generic name:	ezetimibe
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lipitor

Generic name:	atorvastatine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-03-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-12-2014
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-11-2016
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-10-2017
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	EUCTR2013-000935-29-NL
CCMO	NL46854.018.14