A Double-Blind, Placebo Controlled, Multicenter Study to Assess the Effect of Evolocumab on Cognitive Function in Patients with Clinically Evident Cardiovascular Disease and Receiving Statin Background Lipid Lowering Therapy: A Study for Subjects Enrolled in the FOURIER (Study 20110118) Trial

Published: 24-12-2015
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Main objective:To evaluate change over time in executive function, as assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory (SWM) strategy index of executive function, in subjects receiving statin...

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

Summary

ID

NL-OMON53170

Source
ToetsingOnline

Brief title
EBBINGHAUS

Condition

- Cardiac disorders, signs and symptoms NEC

Synonym
dyslipidemia, elevated cholesterol

Research involving
Human

Sponsors and support

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

Intervention

Keyword: cardiovascular disease, cognitive function, dyslipidemia, evolocumab

Outcome measures

Primary outcome

Primary endpoint:

SWM strategy index of executive function

Timepoint(s) of evaluation of this end point:

From baseline assessment to end of study visit assessment

Secondary outcome

Secundary endpoints:

- SWM between-errors score

- PAL total errors adjusted

- RTI median 5-choice reaction time

Timepoint(s) of evaluation of this end point:

From baseline assessment to end of study visit assessment

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.

Statins have been shown to lower the blood levels of LDL-C (low-density lipoproteïne-cholesterol, *bad* cholesterol). Effects of statins on memory and cognitive function have been investigated in several studies, but the overall evidence available today is inconclusive. There are a number of meta analyses (studies that combine data from many individual studies) that suggest that statins have either no effect or a beneficial effect on cognitive function en next to that there are some individual reports and smaller studies that suggest a negative impact of statins.

So far, completed Amgen studies have included a total of over 6000 study participants and do not suggest any negative effects of evolocumab on memory or cognitive function. This includes longer-term studies lasting 1 year or longer. However, because this is an issue of interest to medical doctors, patients, and regulatory authorities, the Sponsor has designed the EBBINGHAUS study (Study 20130385).

Study objective

Main objective:
To evaluate change over time in executive function, as assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory (SWM) strategy index of executive function, in subjects receiving statin therapy in combination with evolocumab, compared with subjects receiving statin therapy in combination with placebo.

Secondary objectives:
To evaluate change over time in subjects receiving statin therapy in

combination with evolocumab, compared with subjects receiving statin therapy in combination with placebo in the following:
- Working memory, as assessed by the CANTAB Spatial Working Memory (SWM) test between-errors score
- Memory function, as assessed by the CANTAB Paired Associated Learning (PAL) test
- Psychomotor speed, as assessed by the CANTAB Reaction Time (RTI) test

Study design

Phase 3, multicenter, double-blind, placebo controlled, parallel group.
Lipid lowering background therapy including a statin.

Randomisation in FOURIER (1:1):
- AMG145 (Q2W or Q4W, subject is allowed to choose during the study)
- placebo (Q2W or Q4W, subject is allowed tio choose during the study)

Signed Informed Consent, after which Screening will take place, followed by Randomisation if applicable. IP-adminstration according to FOURIER-protocol (20110118 - see above), Follow Up (with visites for the EBBINGHAUS-study during week 24 (+/- 6 weeks), week 48 (+/- 6 weeks), thereafter every 48 weeks (+/- 6 weeks). In addition, assessments will be completed each time a subject reports a neurocognitive adverse event in Study 20110118.End of Study-visit will take place during the End of Study-visit of the FOURIER-study or within 6 weeks prior to the End of Study-visit for the FOURIER study.
Participation in the EBBINGHAUS study can be for as long as the duration of the FOURIER study (it s expected for a period of max. 4 years).

At least approximately 2000 patients, up to 4000 patients.
De study ends in accordance with the FOURIER study (20110118).

Intervention

At each visit the subject will complete the following 3 different CANTAB (Cambridge Neuropsychological Test Automated Battery)
tests on a touch screen computer (tablet computer) at the study site.
- Spatial Working Memory (SWM)
- Paired Associates Learning (PAL)
- Reaction Time (RTI)

Study burden and risks

No investigational drugs will be administered to the subjects as part of the participation in the EBBINGHAUS study.
Therefore, potential risks to being in the EBBINGHAUS study are only from the procedures of the computerized cognitive (brain thinking) function tests.

The risks for participation in this study are minimal (see the answer to question E9).

Contacts

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Trial sites

Listed location countries

Australia, Belgium, Canada, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Italy, Japan, Latvia, Malaysia, Netherlands , New Zealand, Norway, Poland, Portugal, Russian Federation , Singapore, Slovakia, South Africa, Spain, Sweden, Taiwan (Province of China), Turkey, United Kingdom, United States of America

Eligibility criteria

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

Inclusion criteria

1) Signed informed consent for Study 20130385
2) Randomized into Study 20110118 (FOURIER)

Exclusion criteria

1) Current or known past diagnosis of dementia or mild cognitive impairment (MCI);2) Any condition or situation, including other significant mental or neurological disorders that, in the investigator*s opinion, may confound the study results, or may interfere significantly with the subject*s participation in Study 20130385 or in Study 20110118

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):	12-02-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	31-12-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-02-2015
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:	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	2014-001976-75
ClinicalTrials.gov	NCT02207634
CCMO	NL50180.060.14