PHASE 3 MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP EVALUATION OF THE EFFICACY, SAFETY, AND TOLERABILITY OF BOCOCIZUMAB (PF-04950615), IN REDUCING THE OCCURRENCE OF MAJOR CARDIOVASCULAR EVENTS IN HIGH RISK SUBJECTS - SPIRE 1

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Primary objective The primary objective of this clinical trial is to demonstrate the superior efficacy of bococizumab compared with placebo in reducing the risk of major CV events, a composite endpoint which includes adjudicated and confirmed CV...

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

Summary

ID

NL-OMON44718

Source
ToetsingOnline

Brief title
9002/0154 (B1481022)

Condition

- Lipid metabolism disorders

Synonym
cardiovascular disease; dyslipidemia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: cardiovascular disease, Double-blind randomized controlled trial, PF-04950615, Phase 3

Outcome measures

Primary outcome

The primary endpoint is defined as the time from randomization to the first adjudicated and confirmed occurrence of a major CV event, a composite endpoint that includes CV death, non fatal MI, non fatal stroke, and hospitalization for unstable angina needing urgent revascularization. (as defined in Appendix 4 of the protocol).

Secondary outcome

Key Secondary Endpoints

Key secondary endpoints are defined as the times from randomization to the first adjudicated and confirmed occurrence of:

* A composite endpoint of CV death, non fatal MI, and non fatal stroke;

* A composite endpoint of all-cause death, non fatal MI, non fatal stroke, and hospitalization for unstable angina needing urgent revascularization;

* A composite endpoint of all cause death, non fatal MI and non fatal stroke;

* Hospitalization for unstable angina needing urgent revascularization.

Other Secondary Clinical Endpoints

The times from randomization to the first adjudicated and confirmed occurrence of the following endpoints:

* A composite endpoint of CV death, non fatal MI, and non fatal stroke, and hospitalization for unstable angina;
* CV death;
* Any MI (fatal and non-fatal);
* Fatal MI;
* Non fatal MI;
* Any stroke (fatal and non-fatal);
* Any stroke (fatal and non-fatal), of any etiology;
* Fatal stroke;
* Non-fatal stroke;
* Hospitalization for unstable angina;
* Hospitalization for congestive heart failure (CHF);
* Any coronary revascularization procedure;
* CABG;
* PCI;
* Any arterial revascularizations;
* All-cause death.

Other Secondary Circulating Biomarker Endpoints

The LDL-C (direct measure) biomarker endpoints are the percent and nominal change from baseline at Week 14 and the percent change from baseline to the

last available post randomization measure.

Other lipid endpoints include the percent change from baseline at Week 14 in levels of:

* Non HDL C;

* Total cholesterol;

* VLDL C;

* RLP-C;

* Apo B;

* Lp(a);

* Triglycerides;

* HDL-C;

* Apo A I.

Safety Endpoints

Safety endpoints include investigator reported adverse events, (including Type 1 and 3 hypersensitivity reactions and injection site reactions), serious adverse events, vital signs, examination observations (physical and neurological examinations and cognitive testing), 12 lead ECG recordings, and safety laboratory tests, including hematology, blood chemistry studies (including liver function tests and creatine kinase tests), urinalysis studies, and ADA assessments. See Section 7.2 for details.

Study description

Background summary

Bococizumab (PF-04950615, previously numbered as RN316 or J16) is a humanized monoclonal antibody against the proprotein convertase subtilisin kexin type 9 (PCSK9) enzyme responsible for the regulation of the low density lipoprotein receptor (LDLR), being developed for the following indications: (1) the treatment of primary hyperlipidemia or mixed dyslipidemia and (2) cardiovascular (CV) risk reduction, in subjects at high and very high risk of major cardiovascular events.

Cardiovascular disease (CVD) due to atherosclerosis continues to be the leading single cause of death in industrialized countries. High serum lipid levels, and especially high low density lipoprotein cholesterol (LDL-C) levels, have been demonstrated to strongly and directly correlate with cardiovascular disease risks by numerous epidemiological studies. Moreover, large prospective clinical outcome trials have demonstrated that lowering LDL-C decreases cardiovascular morbidity and mortality.45 Despite the availability of highly effective lipid lowering therapies such as statins and ezetimibe, a significant percentage of patients remain at high risk for CVD.

PCSK9 is the ninth member of the subtilisin family of kexin like proconvertases to be identified14 and is closely related to proteinase K. PCSK9 is linked to serum LDL-C levels by binding to and down regulating LDLR levels on hepatocytes. This reduction in LDLR results in reduced cellular uptake of LDL-C and, consequently, higher LDL-C levels in serum.17 In contrast, a decrease in active PCSK9 leads to an increase in hepatocyte LDLR, causing an increase in LDL uptake from circulation and consequently a subsequent reduction in serum LDL-C levels.15,16 Loss of function mutations lead to higher levels of the LDLR, and consequently lower plasma LDL-C levels, and protection from coronary heart disease.18,19,20,21,22 This loss of PCSK9 appears to have no discernible adverse consequences in the affected subjects.21,22

Bococizumab targets the evolutionarily conserved LDLR binding domain of PCSK9 with high affinity. Bococizumab administered either as a single or multiple doses, either alone or in combination with current lipid lowering agents, was generally well tolerated in completed studies. No subjects in completed studies met the categorical criteria of drug-induced liver injury according to the Hy*s law definition. Seven percent of subjects (37/517) exposed to bococizumab across all completed studies developed anti-drug antibodies (ADAs). The presence of ADAs was not associated with clinical signs or symptoms of hypersensitivity.

Study objective

Primary objective
The primary objective of this clinical trial is to demonstrate the superior

efficacy of bococizumab compared with placebo in reducing the risk of major CV events, a composite endpoint which includes adjudicated and confirmed CV death, non fatal MI (myocardial infarction), non fatal stroke, and hospitalization for unstable angina with urgent revascularization (as defined in Appendix 4 in the Protocol), in subjects at high or very high risk of major CV events, who are on background lipid lowering treatment, and have an LDL-C * 70 mg/dL (1.81 mmol/L) or non-HDL-C (non-high density lipoprotein cholesterol) * 100 mg/dL (2.59 mmol/L).

Clinical Secondary Objectives
The key secondary objectives of this clinical trial are to demonstrate in subjects with high or very high risk of major CV events, who are on background lipid lowering treatment, and have an LDL-C * 70 mg/dL (1.81 mmol/L) or non-HDL-C * 100 mg/dL (2.59 mmol/L), the superior efficacy of bococizumab compared with placebo in reducing the risk of adjudicated and confirmed key secondary endpoints:
*A composite endpoint of CV death, non-fatal MI, and non-fatal stroke;
* A composite endpoint of all-cause death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization;
* A composite endpoint of all-cause death, non-fatal MI and non-fatal stroke;
* Hospitalization for unstable angina needing urgent revascularization.

Please refer to Protocol Section 2.1.2 for additional secondary objectives.

Study design

This is an event driven, Phase 3 multi center, double blind, randomized parallel group evaluation of the efficacy, safety, and tolerability of bococizumab compared with placebo, in reducing the occurrence of major CV events in subjects at risk, who are on background lipid lowering treatment and have an LDL-C * 70 mg/dL (1.81 mmol/L) or non-HDL-C *100 mg/dL (2.59 mmol/L). After obtaining informed consent, there will be a pre-screening visit. At this visit subjects will have consented to have had lipid levels assessed and to provide medical records for review, only, so as to determine if the subject qualifies for this study. The interactive response technologies (IRT) system will determine if the subject is eligible for the study or if the subject should be screen failed. This will be followed within 30 days by a screening visit, and a run-in period up to 6 weeks, during which subjects will be fully assessed with respect to the trial enrollment criteria and compliance with the self-administration of subcutaneous injections. The run-in period will be followed by the treatment period, the duration of which will be determined by the number of subjects with primary endpoint events, and concluded by a safety follow-up period.

Approximately 85,000 subjects may be screened and approximately 17,000 subjects will be randomized. The study will be conducted in North America, Latin America, Europe, Africa, Asia, and Australia in approximately thirty countries.

After randomization to PF 04950615, subjects will receive 150 mg every two weeks (Q2wks), or placebo, in a 1:1 ratio.

The trial is intended to complete when approximately 844 subjects have accrued adjudicated and confirmed primary endpoint events, or 12 months following the randomization date of the last subject, whichever occurs later. Potential endpoint events will be adjudicated by an independent adjudication committee. Subject safety will be monitored by an independent data monitoring committee (DMC). An independent statistical data analysis center will provide analyses to the DMC according to the DMC*s charter.

Intervention

Subjects will be randomized to PF-04950615 150 mg or placebo Q2wks in a 1:1 ratio. Subjects will self-inject, or if unable to self-inject, have investigational product administered by a caregiver (eg, a family member or health care assistant).

Study burden and risks

The potential benefit of participation in this study for all subjects in this study is close monitoring of their medical condition and safety. Those randomized to the active treatment arm may have a benefit of a lower risk of major CV events. Those randomized to the placebo arm are not expected to obtain any additional benefit, beyond close monitoring of their medical condition and safety. A potential risk of participation, for all subjects, is the occurrence of injection site reactions. For those receiving active treatment, there may be an additional risk of achieving a very low LDL-C. It is not known if there are any risks associated with very low LDL-C.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:
1. Informed Consent
There must be evidence of personally signed and dated, informed consent documents for both the pre-screening and screening visits indicating that the subject has been informed of all pertinent aspects of the study. The pre-screening visit informed consent form will be limited to study activities up until the screening visit. The screening visit informed consent form will cover all aspects of the study. Subjects should be reconsented if there are modifications to the original informed consent document, at the next available opportunity.;2. Compliance
Subjects must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.;3. Age
Subjects who have had a prior CVD event, subjects must be men or women age * the legal age of majority (legal adulthood), in the subject*s country. Subjects who have not had a prior CVD event must be age * 50 years, if a man, and must be age * 60 years, if a woman, with the
following exceptions:
Subjects who have not had a prior CVD event, but who have a condition of elevated LDL-C, (heterozygous familial hypercholesterolemia [heFH] or a history of LDL-C*190 mg/dL [4.9 mmol/L]) should be * 35 years of age if a man, and * 45 years of age, if a woman.;4. Acceptance of administration of investigational Product
Subjects must be willing and able to self-administer or be administered sub-cutaneous injections of investigational product.;5. Requirements for background lipid lowering treatment
There should be no plans at the time of pre-screening and randomization to modify the dose of statin for the duration of the trial. Unless the background lipid lowering treatment exceptions described below are met, subjects must be treated with one of the following highly effective statins at the specified daily doses for * 6 weeks prior to the pre-screening visit:

* atorvastatin, at least 40 milligrams (mg) once a day;
* rosuvastatin, at least 20 mg, once a day;
* simvastatin, at least 40 mg, once a day or, if a subject has been on that dose for > 1 year, 80 mg, once a day.
Combination medications that contain atorvastatin, rosuvastatin, or simvastatin components described at the aforementioned doses will be permitted. ;Background lipid lowering treatment exceptions
The following background lipid lowering treatment exceptions are permitted:
* Lower doses of statins due to partial statin intolerance
Subjects may be on a lower dose of one of the highly effective statins described above if there is documented intolerance to any one of them (atorvastatin, rosuvastatin, or simvastatin) at the aforementioned, or lower, doses.
Intolerance to any dose of any statin must be documented as historical adverse events attributed to the statin in question, in the source documentation and case report form (CRF).
* Regulatory limitations
Subjects may be on a lower dose of one of the highly effective statins described above if the highest locally approved dose for one of the stated statins is lower than those doses shown above (e.g., in Japan, atorvastatin 20 mg, once a day, is the highest locally approved dose) or due to label restrictions.
* Alternative statins
Subjects may be treated with other statins (pravastatin, fluvastatin, pitavastatin, or lovastatin), different from the highly effective statins listed above, if there is documented intolerance to any two different highly effective statins (atorvastatin, rosuvastatin, simvastatin) at the lowest available dose, for at least one of those highly effective statins.
Intolerance to any statin must be documented as historical adverse events attributed to the statin in question, in the source documentation and CRF.;6. Qualifying cardiovascular disease risk
Qualifying cardiovascular disease (CVD) risk must be documented by supporting source documentation such as, but not limited to, copies of a hospital discharge summary, copies of medical records, or other documents that can be used to confirm the qualifying CVD risk event or diagnosis and its approximate date of occurrence or onset. Ideally, this documentation should be acquired before Visit 1. A subject may qualify for inclusion according to the following (see Appendix 10):
a. Myocardial infarction
b. Ischemic stroke
c. Coronary artery revascularization
d. Prior non-coronary arterial revascularization
e. CVD risk conditions
* Subjects may qualify for inclusion if they have two CVD risk conditions;
OR
* one CVD risk condition and two CV risk factors (described below);
OR
* a condition of elevated LDL-C as specified below:;CVD Risk Conditions:
- Diabetes
- Peripheral vascular disease
- Chronic kidney disease
- Condition of elevated LDL-C;CVD risk factors:

* Imaging evidence of significant coronary artery disease
* Smoking
* Low levels of HDL-C
* Elevated levels of hs-CRP
* Microabluminuria
* Lipoprotein (a);7. Qualifying lipids level (LDL-C or non- HDL-C);8. Contraception requirements;See Protocol Section 4.1 for further details of each inclusion criteria.

Exclusion criteria

Subjects presenting with any of the following will not be included in the study:Personnel involved in the conduct of the study: ;1. Subjects who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees directly involved in the conduct of the trial.;2. Exclusionary prior CV events or planned revascularization procedures
-A planned coronary (PCI or CABG) or other arterial revascularization.
-Myocardial infarction, stroke, or any non-coronary artery revascularization * 30 days prior to screening,
-Coronary revascularization * 90 days prior to screening;
- Subjects with SAEs that would have potentially met the criteria for a CVD event (as defined in Appendix 4), between Visit 0 and Visit 5, should be excluded. Such subjects may be rescreened at a later date.;3. Participation in prior clinical research studies
Participation in other studies involving small molecule investigational drug(s) (Phases 1-4) within 1 month, or five half-lives, of Visit 1, whichever is longer; any participation in a cholesteryl ester transfer protein (CETP) inhibitor trial within 1 year of Visit 1; or any biological agents within 6 months or 5 half-lives, of Visit 1, whichever is longer (the investigator should refer to documents provided by the subject on the other study to determine the investigational product half-life). If the blind of the prior study has been broken and the investigator provides documentation that the subject received placebo, the potential subject can be included, regardless of when participation occurred.;4. Other exclusionary conditions.
Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.;5. Childbearing potential and/or breast feeding
Pregnant female subjects; breastfeeding female subjects; and male subjects with partners currently pregnant who are sexually active; male subjects able to father children and female subjects of childbearing potential, who are at risk of pregnancy with their partners and are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for 63 days after last dose of investigational product (refer to Section 4.4.2).;6. Latex sensitivity
Latex sensitive individuals (due to potential for exposure to natural dry rubber in the pre-filled syringe cap of investigational product, during administration).;7. Apheresis

Undergoing lipid apheresis, within 6 weeks of pre-screening, or planned start of lipid apheresis.;8. Severe congestive heart failure
Congestive heart failure of New York Heart Association (NYHA) Class IV, or if there is prior documentation of left ventricular ejection fraction (LVEF) of < 25%, measured by imaging. For subjects who have had serial assessments of LVEF, only the most recent study is used for the
purposes of this exclusion requirement.;9. Dialysis
Potential subjects with end stage renal disease on dialysis.;10. Chronic renal insufficiency
Potential subjects with an eGFR of < 30 ml/min/1.73m2 by MDRD formula at Visit 1.;11. Hypertension
Poorly controlled hypertension at any screening visit or at randomization, defined as the average of two systolic blood pressure (BP) measurements > 180 mmHg or the average of two diastolic BP measurements > 110 mmHg even with treatment. Subjects who have hypertension and are controlled on stable doses of anti-hypertensive medications may be included. An additional BP measurement may be performed within the hour or at the completion of the office visit, to confirm a reading.;12. Cerebral hemorrhage risk
A prior history of hemorrhagic stroke or lacunar infarct resulting in a stroke (a lacunar infarct which was seen with cerebral imaging is not exclusionary in the absence of a clinical stroke). A prior ischemic stroke which resulted in hemorrhagic transformation is not exclusionary.;13. Tissue donation
Plans to donate any tissues (eg, blood, sperm, or other tissues, including participating in in vitro fertilization) during the study.;14. Substance abuse
Current history of alcoholism or drug addiction according to diagnostic and statistical manual of mental disorders (DSM) IV criteria within 12 months prior to screening. Use of any recreational drugs within 12 months prior to screening.;15. Human immunodeficiency virus
Medical history of positive testing for human immunodeficiency virus (HIV).;See Protocol Section 4.2 for exclusion criterions 16-23

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):	25-03-2014
Enrollment:	764
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BOCOCIZUMAB (PF-04950615)

Ethics review

Approved WMO Date:	08-11-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-12-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-09-2014
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-12-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-01-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-01-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-02-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-03-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-04-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	13-04-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-04-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-05-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-05-2015
Application type:	Amendment
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Approved WMO Date:	19-05-2015
Application type:	Amendment
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Approved WMO Date:	30-06-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-07-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	19-08-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-10-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-10-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-12-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-12-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-01-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-02-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-04-2016

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-04-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-06-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2013-002646-36-NL
CCMO	NL46221.056.13