A 52 WEEK, PHASE 3 DOUBLE-BLIND, RANDOMIZED, PLACEBOCONTROLLED, PARALLEL-GROUP STUDY TO ASSESS THE EFFICACY, SAFETY AND TOLERABILITY OF PF-04950615 IN SUBJECTS WITH PRIMARY HYPERLIPIDEMIA OR MIXED DYSLIPIDEMIA AT RISK OF CARDIOVASCULAR EVENTS

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

Summary

ID

NL-OMON42129

Source
ToetsingOnline

Brief title
B1481045 (9002/0263)

Condition

- Lipid metabolism disorders

Synonym
Primary hyperlipidemia; high blood cholesterol

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Double-blind randomized trial, PF-04950615, Phase III, Primary hyperlipidemia

Outcome measures

Primary outcome

The primary endpoint of this study is the percent change from baseline in

fasting LDL-C at week 12.

Secondary outcome

Key secondary endpoints are

1) Percent change from baseline in fasting TC, ApoB, and non HDL-C at week 12;

2) Percent change from baseline in fasting LDL-C at week 12 in subjects with

primary hyperlipidemia or mixed dyslipidemia (pre-randomization TG < or >=200

mg/dL [2.26 mmol/L]);

3) Percent change from baseline in fasting lipoprotein(a) (Lp(a)) at week 12

and 4) Percent change from baseline in fasting HDL-C at week 12. Fasting

LDL-C, TC, ApoB, non HDL-C, Lp(a) and HDL-C are secondary endpoints at weeks 24

and 52.

Secondary endpoints include percent change from baseline at week 12, 24 and 52

in fasting Apolipoprotein A-I (ApoA-I), Apolipoprotein A-II (ApoA-II), TG, VLDL-C, along with absolute change from baseline at week 12, 24, and 52 in TC/HDL-C and ApoB/ApoA-I ratios, along with absolute change from baseline at week 12 in LDL-C, TC, ApoB, non HDL-C, Lp(a), and HDL-C, safety and tolerability and immunogenicity of PF 04950615, and plasma PF-04950615 concentrations. Safety endpoints include: adverse events (including Type 1 and 3 hypersensitivity reactions and injection site reactions) and anti-drug antibodies (ADAs).

Study description

Background summary

PF-04950615 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 treatment of primary hyperlipidemia and mixed dyslipidemia.

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. Despite the availability of lipid lowering therapies such as statins and ezetimibe, a significant percentage of subjects at high risk for CVD fail to reach or maintain their LDL-C treatment target. Serum LDL-C levels can be effectively modulated via the cellular uptake of LDL particles through the LDLR which are primarily expressed by hepatocytes.

PCSK9 is the ninth member of the subtilisin family of kexin like proconvertases to be identified 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. 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. Loss of function mutations lead to higher levels of the LDLR, and consequently lower plasma LDL-C levels, and protection from coronary heart disease. This loss of PCSK9 appears to have no discernible adverse consequences in the affected subjects.

PF-04950615 is a humanized monoclonal antibody targeting the evolutionarily conserved LDLR binding domain of PCSK9 with high affinity. In total, 517 subjects (as of 1 December 2013) have received at least one dose of PF 04950615 in completed studies. PF-04950615 administered either as single or multiple dose, both alone or in combination with current lipid lowering agents, was generally well tolerated. Results from the interim analysis of the on-going Phase 2b study (Study B1481015) showed that PF-04950615 was generally well tolerated at each dose, with an adverse event profile similar to previous findings in the clinical program, and clear evidence of efficacy was established in all PF 04950615 treatment groups.

Study objective

A complete list of objectives is presented in Section 2.1 Objectives of the Study Protocol. In summary, the primary objective of this study is to demonstrate a superior LDL-C lowering effect of PF 04950615 150 mg administered by the SC route Q2wks compared to placebo, in subjects with primary hyperlipidemia or mixed dyslipidemia at high or very high risk for cardiovascular (CV) events receiving statin therapy and whose LDL C is >=100 mg/dL (2.59 mmol/L). Secondary objectives are to demonstrate a superior effect of PF-04950615 on Total cholesterol (TC), High density lipoprotein cholesterol (HDL-C), Triglycerides (TG), and non HDL-C; other lipid parameters, including Apolipoprotein B(ApoB), ApoA-I, ApoA II, lipoprotein a (Lp(a)); and very low density lipoprotein cholesterol (VLDL-C) in subjects with primary hypercholesterolemia (pre-randomization triglycerides (TG) <200 mg/dL (2.26 mmol/L) and, in subjects with mixed dyslipidemia (pre-randomization TG >=200 mg/dL (2.26 mmol/L). Safety, tolerability and pharmacokinetics of PF-01950615 will be characterized.

Study design

This study is a 52 week, Phase 3, double blind, placebo controlled, randomized, stratified, parallel group, multi center clinical trial designed to compare the efficacy, safety and tolerability of PF 04950615 150 mg SC Q2wks to placebo for LDL C lowering in subjects with primary hyperlipidemia or mixed dyslipidemia at high or very high risk for CV events. The study will randomize a total of approximately 690 subjects in a 2:1 ratio (approximately 460 and 230 subjects in the PF-04950615 arm and placebo arm respectively), who will receive study drug for 12 months.

After providing consent, subjects will enter a screening period of approximately 28 days to verify eligibility for the trial. Eligible subjects will be considered enrolled and progress to the Randomization visit. Results from screening evaluations will be reviewed and only subjects who continue to meet all eligibility criteria will be randomized. Randomized subjects will enter the 52-week treatment period, followed by a 6 week follow-up, for a total of 58 weeks study participation.

Intervention

Subjects will be randomized to PF-04950615 150 mg or placebo Q2wks in a 2:1 ratio. Subjects will self-inject, or if unable to self-inject, have study drug administered by a family member or home caregiver. Study site personnel will be allowed to administer study drug after randomization only under extreme exceptional circumstances if neither the subject nor the home caregiver or family member are able to do the injection.

Study burden and risks

The benefit of participation for all subjects in this study, is close monitoring of their medical condition and safety of their treatment. Those randomized to the active treatment arm may have a benefit of a lower risk of cardiovascular (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, which may itself be associated with improving lipid levels. 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 maintaining a very low LDL C for a short time. It is not known if there are any risks associated with very low LDL C but none have been identified in this programme to date.

For an overview of the expected risks and side-effects please see the subject information sheet.

Contacts

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Pfizer

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Scientific
Pfizer

East 42nd street 235
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator*s study team before subjects are included in the study.
Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:
1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
2. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
3. Males and females >= 18 years of age where permitted by law.
4. With primary hyperlipidemia or mixed dyslipidemia.
5. For all clinical sites except for those in the Netherlands: Subjects must be on a stable dose of either simvastatin 40 mg or higher, rosuvastatin 10 mg or higher, atorvastatin 20 mg or higher, or pravastatin 40 mg or higher for at least 6 weeks prior to screening.
- There should be no plans at the time of screening and randomization to modify the dose of statin for the duration of the trial.;For clinical sites in the Netherlands only: Subjects must be on a maximally tolerated stable dose of either simvastatin, rosuvastatin, atorvastatin or pravastatin for at least 6 weeks prior to screening. No dose should be lower than simvastatin 40 mg, rosuvastatin 10 mg, atorvastatin 20 mg or pravastatin 40 mg.
- There should be no plans at the time of screening and randomization to modify the dose of statin for the duration of the trial.
- The maximally tolerated dose is either the highest dose the subject can tolerate or the highest dose the investigator determines can be safely prescribed.;6. Subjects should be at high or very high risk of incurring a CV event, defined as:

a. Known CVD or CVD risk equivalents:
- Known history of CVD.
- Coronary heart disease: history of acute myocardial infarction, or evidence of silent myocardial infarction or myocardial ischemia, or history of unstable angina and stable angina pectoris, or history of coronary procedures (coronary angioplasty and coronary artery surgery), or;
- Other clinical atherosclerotic diseases: peripheral arterial disease, or abdominal aortic aneurysm, or carotid artery disease (symptomatic [eg, transient ischemic attack or stroke of carotid origin] or >50 percent stenosis on angiography or ultrasound), or likely other forms of clinical atherosclerotic disease (eg, renal artery disease), Type 2 or Type 1 diabetes, or;
- Chronic kidney disease (CKD), defined as glomerular filtration rate (GFR) calculated by Modification of Diet in Renal Disease (MDRD) formula between 30 and 60 mL/min/1.73m2 (inclusive).
b. Presence of multiple risk factors:
Subjects who do not have past CVD disease or CVD risk equivalents but have 3 or more of the risk factors from the list below:
- Current cigarette smoking defined as any smoking for 30 days or more at the time of screening.
- HDL-C <40 mg/dL (<1.0 mmol/L) at screening or TC/HDL-C ratio>/=6.
- Family history of premature Coronary Heart Disease (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years).
- Age (men >=55 years; women >=65 years).
- hs-CRP >2.0 mg/L at screening.
7. Lipids should meet the following criteria on a background treatment with a statin:
- Fasting LDL-C >=100 mg/dL (2.59 mmol/L) at 2 screening visits (screening visits S1 and S3) and the value at the third screening visit (S3) within 7 days (±3 days) of randomization must not be lower or higher than 20% of this initial value (in order to control the variability related to the fasting LDL-C assay), as described in Section 7.1.
Note: If fasting LDL-C at screening visit S3 is lower or higher than 20% of the initial value, LDL-C can be repeated once (within 7 days of randomization), and the subject is eligible if the value of this repeat test is within 20% (inclusive) of the value at screening visit S3.
- All subjects must have fasting TG <=400 mg/dL (4.51 mmol/L) at the third screening visit (S3).
8. Male and female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 63 days after the last dose of assigned treatment. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active (Section 4.4.2).
Female subjects who are not of childbearing potential (ie, meet at least one of the following criteria):
- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure or;
- Achieved post-menopausal status, defined as: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicule-stimulating hormone (FSH) level within the laboratory*s reference range for postmenopausal females.

Exclusion criteria

Subjects presenting with any of the following will not be included in 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. Participation in other studies involving small molecule investigational drug(s) (Phases 1-4) within 1 month or 5 half lives, whichever is longer, except for cholesteryl ester transfer protein (CETP) inhibitors (indefinitely), or biological agents within 6 months or 5 half lives, whichever is longer before the current study begins and/or during study participation (the investigator should refer to documents provided by the subject on the other study to determine the investigational product half life). If the blind has been broken and the Investigator knows (with documentation) that the subject received placebo, he/she can be included.;3. Subjects with prior exposure to PF-04950615 or other investigational PCSK9 inhibitor.;4. Subjects who are unable to receive injections, as either a self-injection, or administered by a family member, or home caregiver.;5. History of a cardiovascular or cerebrovascular event or procedure (eg, myocardial infarction, stroke, transient ischemic attack, angioplasty) during the past 90 days.;6. Congestive heart failure, New York Heart Association functional class IV, or Left Ventricular Ejection Fraction measured by imaging <25%.;7. Poorly controlled hypertension at any screening visit or at randomization (defined as the average of two systolic blood pressure measurements greater than 160 mm Hg or the average of two diastolic blood pressure measurements greater than 100 mm Hg, even with treatment). Subjects who have hypertension and are controlled on stable dosages of anti hypertensive medications can be included. An additional blood pressure (BP) may be performed within the hour or at the completion of the office visit, to confirm a reading.;8. History of hemorrhagic stroke or lacunar infarct.;9. Current untreated hypothyroidism or thyroid stimulating hormone (TSH) > upper limit of normal (ULN) at screening. Subjects who are treated and well controlled should be on the stable dose of thyroid hormone for at least 6 months.;10. Current history of alcoholism or drug addiction according to the 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.;11. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer resolved by excision).;12. Medical history of positive testing for Human immunodeficiency virus (HIV).;13. Any disease or condition that might compromise the hematological, renal, hepatic, pulmonary, endocrine, central nervous, immune, or gastrointestinal systems (unless deemed not clinically significant by the Investigator and/or the Sponsor) or confound the interpretation of the study results. Examples of such conditions include but are not limited to nephrotic syndrome, uncontrolled diabetes, excessive alcohol consumption, cholestatic liver disease, unstable mental illness.;14. Use of statins other than atorvastatin, rosuvastatin, simvastatin, pravastatin or use of red yeast rice.;15. Undergoing apheresis or have planned start of apheresis.;16. Initiation of, or change in, non lipid lowering prescription drugs, herbal medicine or supplements (including foods with added plant sterols and stanols) within 6 weeks of screening (exception: initiation or change in multivitamins used for general health purposes are acceptable). Short term use of medications to treat acute conditions, and vaccines are allowed (e.g., antibiotics or allergy medication).;17. Subjects on systemic corticosteroids (ie, oral, intravenous (IV), intramuscular (IM), or intra-articular. The use of corticosteroids by

inhalation, topical or ophthalmological is permitted. Subjects receiving topical preparations at high concentrations over large body areas for a long period of time should be discussed with the medical monitor.;18. Subjects taking prescription medications that are contraindicated with the use of statins. Refer to statin product labels for these medications.;19. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (IgG protein) or molecules made of components of monoclonal antibodies (eg, Enbrel® which contains the Fc portion of an antibody or Lucentis® which is a Fab).;20. Subjects who are latex-sensitive (due to potential for exposure to latex or dry rubber in the pre-filled syringe cap during self administration).;21. Any abnormal hematology values, clinical chemistries, urinalysis, or ECGs judged by the Investigator as clinically significant.;For exclusion conditions 22-29 please refer to the protocol

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):	26-03-2015
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PF-04950615

Ethics review

Approved WMO Date:	03-11-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-01-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-02-2015
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:	10-03-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-04-2016
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	EUCTR2014-000478-20-NL
CCMO	NL48630.056.14