A 52 WEEK, PHASE 3 DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED,PARALLEL-GROUP STUDY TO ASSESS THE EFFICACY, SAFETY AND TOLERABILITY OF PF-04950615 IN SUBJECTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

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

Summary

ID

NL-OMON40591

Source
ToetsingOnline

Brief title
9002/0157 (B1481021)

Condition

- Lipid metabolism disorders

Synonym
Heterozygous familial hypercholesterolemia; high blood cholesterol

Research involving
Human

Sponsors and support

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

Intervention

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

Outcome measures

Primary outcome

The complete list of study endpoints is presented in the Endpoints section of the protocol. In summary, the primary endpoint of this study is the percent change from baseline in fasting LDL-C at 12 weeks following randomization.

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 Lp(a) at week 12 and 3) 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. Other secondary endpoints are: fasting Apolipoprotein A-I (ApoA-I), Apolipoprotein A-II (ApoA-II), very low density lipoprotein (VLDL-C), TG, TC/HDL-C and ApoB/ApoA-I ratios, proportion of subjects with fasting LDL-C <=100 mg/dL (2.6 mmol/L) and <=70 mg/dL (1.8 mmol/L), plasma PF-04950615 concentrations, these will be will be assessed at week 12, 24 and 52. 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 degradation 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 CVD risks by numerous epidemiological studies. Moreover, large prospective clinical outcome trials have demonstrated that lowering LDL-C decreases cardiovascular morbidity and mortality. Familial hyperlipidemia (FH) is an autosomal dominant inherited genetic disorder of lipoprotein metabolism. Heterzygous familial hypercholesterolemia (HeFH) is generally considered to have a prevalence of about 1 in 500, although in certain populations the condition is more frequent. Untreated, the majority of affected subjects will have symptomatic coronary disease by the age of 60 years, and half the men and 15% of the women will have died. Despite current treatments many HeFH subjects do not achieve target LDL-C levels. This is likely to be partly due to less than maximal doses of therapy, but it is anticipated in the HeFH population, even with maximal doses of currently available treatments many will not reach LDL-C targets for those at high risk of CVD (<100 mg/dL [2.5 mmol/L]) for subjects without pre-existing CVD and <70 mg/dL (1.81 mmol/L) for subjects with pre-existing CVD).

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, 266

subjects (as of 1 March 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 also 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 the study objectives is presented in the Objectives section of the 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 HeFH and at high and very high risk for CV events receiving a maximally tolerated dose of statin therapy and whose LDL-C is >=70 mg/dL (1.8 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 ApoB, ApoA-I, ApoA-II, lipoprotein a (Lp(a)); and VLDL-C in subjects with HeFH receiving maximally tolerated dose of statin therapy and whose LDL-C is >=70 mg/dL (1.8 mmol/L). Safety, tolerability and pharmacokinetics of PF-04950615 will be described.

Study design

This study is a Phase 3, double blind, placebo controlled, randomized, 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 HeFH. The study will enroll approximately 150 subjects in each of the 2 treatment arms, for a total of approximately 300 subjects randomized at approximately 85 sites, who will receive study drug for 52 weeks.

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 Baseline 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.

Intervention

Subjects will be randomized to PF-04950615 150 mg or placebo Q2wks in a 1:1 ratio. The randomization will be stratified by geographic region. Subjects will self-inject, or if unable to self-inject, have study drug administered by a family member, health care assistant or health care provider. Dose

modifications triggered by LDL-C levels <= 10mg/dL or 0.26 mmol/L (described Background, above) will be conducted through the Interactive Response Technologies (IRT) system to preserve study blind. Safety will be assessed through adverse and serious adverse events, vital signs, physical and neurological examinations, 12-lead ECGs and safety laboratory tests including hematology, urinalysis and blood chemistry studies.

Study burden and risks

The potential 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 achieving a very low LDL-C. It is not known if there are any risks associated with very low LDL-C.

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
New York NY 10017
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 legal 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.;4.With previously diagnosed HeFH phenotype as defined according to the Simon Broome criteria, described in Appendix 2 or a genetic diagnosis of HeFH.;5.Subjects are required to be treated with atorvastatin, simvastatin, or rosuvastatin at the highest locally approved dose. If at a lower dose, there must be documentation that the subject is receiving a maximally tolerated dose of the aforementioned statins; and no dose should be lower than atorvastatin 20 mg, rosuvastatin 20 mg, or simvastatin 40 mg.;•Subjects on simvastatin 80 mg must have been on this dose for >1 year before screening.;•All subjects must be on a stable dose 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.;•Source records and case report form (CRF) must show documentation of the requirements shown above.;6. Subjects without known history of CVD or diabetes or chronic kidney disease (definition below) who are on the highest approved statin dose must have a LDL-C >=100 mg/dL (2.59 mmol/L)(or LDL-C >= 110 mg/dL [2.84 mmol/L]if at the maximally tolerated statin dose). Subjects with known history of CVD or diabetes or CKD (definition below) who are on the highest approved statin dose must have a LDL-C >= 70 mg/dL (1.81 mmol/L) dose (or >= 77 mg [1.99 mmol/L] if at the maximally tolerated statin dose.)
Detailed criteria:
Subjects must meet the following fasting LCL-C minimum levels based on their history of CVD or risk equivalent and statin dose.
*LDL-C must meet these values at both screening visits and the value at the second screening visit within 7 days of randomization 1 must not be lower or higher than 20% of this initial value, as described in Section 7.1. If the fasting LDL-C at the second screening visit 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

for the second screening visit.
• Subjects must also have fasting TG <= 400 mg/dL (4.5 mmol/L) at the second screening visit.
Known history of CVD or risk equivalent is based on any one of the below:
• Coronary heart disease (any of the following conditions): history of acute myocardial infarction, or evidence of silent myocardial infarction or myocardial ischemia, or history of unstable angina and stable angina pectoris, and or history of coronary procedures (coronary angioplasty
orand coronary artery surgery);
• Other clinical atherosclerotic diseases (any one of the following conditions): 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), and or likely other forms of clinical atherosclerotic disease (eg, renal artery disease).
OR
• 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).;7.Lipids should meet the following criteria on a background treatment with a statin at the 2 screening visits:;•Subjects at the highest approved dose of statins described in 5, above:;•Fasting LDL C >=70 mg/dL (1.81 mmol/L) at both screening visits and the value at the second screening visit within 7 days of randomization must not be lower or higher than 20% of this initial value, as described in Section 7.1 of the protocol. ;•Subjects not at the highest approved dose of statins described in 5, above:;•Fasting LDL C >=77 mg/dL (1.99 mmol/L) at both screening visits and the value at the second screening visit within 7 days of randomization must not be lower or higher than 20% of this initial value, as described in Section 7.1. ;•Fasting TG <= 400 mg/dL (4.5 mmol/L) at the second screening visit within 7 days of randomization.;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 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 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 (RN316) or other investigational PCSK9 inhibitors.;4. Subjects who are unable to receive injections, as either a self-injection, or administered by a family member, health care assistant or health care provider.;5. History of a cardiovascular or erebrovascular event or procedure (eg, Myocardial infarction, stroke, transient ischemic attack, angioplasty) during the past 30 days.;6. Congestive heart failure, New York Heart Association (NYHA) 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. Additional blood pressure (BP) may be performed within the hour or at the completion of the office visit, to confirm a reading.;8. Any history of hemorrhagic stroke or lacunar infarct.;9. Current untreated hypothyroidism or thyroid stimulating hormone (TSH) > 1X Upper Limit of Normal (ULN) at screening. Subjects who are treated and well controlled should be on a 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 and cholestatic liver disease. ;14. Use of statins other than atorvastatin, rosuvastatin, simvastatin or use of red yeast rice.;15. Undergoing apheresis or have planned to start 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) at screening. The use of corticosteroids topical, inhaled or ophthalmic is permitted.;18. Subjects taking prescription medications that are contraindicated with the use of statins at screening. 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 electrocardiograms (ECGs) at screening judged by

the Investigator as clinically significant, which could impact on subject safety, were the potential subject to be included in the study or interfere with interpretation of the study results.;For exclusion conditions 22-30 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):	26-02-2014
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	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:	31-03-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-09-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-09-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	13-11-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-11-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-03-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-04-2015
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	EUCTR2013-002644-87-NL
CCMO	NL46222.056.13