A 1-Year, Worldwide, Multicenter, Double-Blind, Randomized, Parallel, Placebo-Controlled Study to Assess the Efficacy and Tolerability of Anacetrapib When Added to Ongoing Statin Therapy With or Without Other Lipid Modifying Medication(s) in Patients with Heterozygous Familial Hypercholesterolemia

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PrimaryObjectives: 1. Evaluate the efficacy of adding anacetrapib 100 mg for 52 weeks relative to placebo on plasma concentrations of LDL-C. 2. Evaluate the safety and tolerability of 52 weeks of treatment with anacetrapib 100 mg.Hypotheses: 1....

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

Summary

ID

NL-OMON39058

Source
ToetsingOnline

Brief title
MK-0859-020

Condition

- Lipid metabolism disorders

Synonym
cholesterol that is too high, Heterozygous Familial Hypercholesterolemia

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Sponsor: Merck

Intervention

Keyword: Anacetrapib, Heterozygous Familial Hypercholesterolemia, Placebo, Statin Therapy

Outcome measures

Primary outcome

The primary efficacy endpoint is the percent change from baseline in LDL-C

using direct

method at Week 52.

Safety and tolerability endpoints such as blood chemistry, hematology, and

vital signs

will be monitored. Clinical adverse experiences, select safety endpoints of

interest and

laboratory values exceeding predefined limits of change will be evaluated.

Secondary outcome

Percent change from baseline HDL-C, Non-HDL-C, Apo B and

Apo-A1 and change from baseline in Lp(a) at Week 52 are efficacy variables

addressing

the secondary hypotheses. Some other endpoints of interest are percent change

from

baseline at Week 52 for TC, TC/ HDL-C, LDL-C/HDL-C, Apo B/Apo A-I, LDL-C/Apo

B, Apo E, percent change from baseline for LDL-C, HDL-C, Apo A-I Apo B, and

change

from baseline Lp(a) at Week 64, proportion patients getting to LDL-C goal of

<70 mg/dL

(secondary prevention) or <100 mg/dL (primary prevention) and also proportion of

patients achieving >= 50% reduction from baseline LDL-C.

Study description

Background summary

HeFH is an autosomal dominant disorder caused by mutations in the low density lipoprotein cholesterol (LDL-C) receptor or apolipoprotein B genes leading to significantly increased levels of LDL-C. This disorder promotes the development of premature atherosclerosis and increases the risk of cardiovascular disease. Patients with HeFH benefit from effective LDL-C reduction with established LDL-C-lowering therapies but the majority do not reach treatment goal for LDL-C <100 mg/dL (2.59 mmol/L). Anacetrapib offers an effective and novel mechanism to lower LDL-C beyond levels achieved with statins with or without other lipid-lowering therapies to enable a greater proportion of patients to achieve LDL-C goal.

Study objective

Primary

Objectives:
1. Evaluate the efficacy of adding anacetrapib 100 mg for 52 weeks relative to placebo on plasma concentrations of LDL-C.
2. Evaluate the safety and tolerability of 52 weeks of treatment with anacetrapib 100 mg.

Hypotheses:

1. Treatment with anacetrapib 100 mg for 52 weeks will lower LDL-C to a greater extent than treatment with placebo.
2. Treatment with anacetrapib 100 mg up to 52 weeks is well-tolerated.

Secondary

Objectives:
1. Evaluate the efficacy of adding anacetrapib 100 mg for 52 weeks relative to placebo on plasma concentrations of HDL-C.
2. Evaluate the efficacy of adding anacetrapib 100 mg for 52 weeks relative to placebo on plasma concentrations of non-HDL-C.
3. Evaluate the efficacy of adding anacetrapib 100 mg for 52 weeks relative to placebo on plasma concentrations of apo B.
4. Evaluate the efficacy of adding anacetrapib 100 mg for 52 weeks relative to placebo on plasma concentrations of apo A-1.
5. Evaluate the efficacy of adding anacetrapib 100 mg for 52 weeks relative to placebo on plasma concentrations of Lp(a).
6. Evaluate the effects of cessation of anacetrapib 100 mg for 12 weeks on LDL-C, HDL-C, non-HDL-C, apo B, apo A-1, and Lp(a).
7. Evaluate the safety and tolerability of anacetrapib 12 weeks after cessation of treatment.

Hypotheses:
1. Treatment with anacetrapib 100 mg for 52 weeks will raise HDL-C to a greater extent than treatment with placebo.
2. Treatment with anacetrapib 100 mg for 52 weeks will lower non-HDL-C to a greater extent than treatment with placebo.
3. Treatment with anacetrapib 100 mg for 52 weeks will lower apo B to a greater extent than treatment with placebo.
4. Treatment with anacetrapib 100 mg for 52 weeks will raise apo A-1 to a greater extent than treatment with placebo.
5. Treatment with anacetrapib 100 mg for 52 weeks will lower Lp(a) to a greater extent than treatment with placebo.

Exploratory

Objectives:
1. Evaluate the effects of anacetrapib (100 mg) relative to placebo on TC/HDL-C, LDL-C/HDL-C, Apo B/Apo A-1, LDL-C/Apo B, Apo E, and lipoprotein sub-fractions after 52 weeks of treatment.
2. Evaluate the proportion of patients reaching LDL-C goal of <70 mg/dL (1.81 mmol/L) (secondary prevention) or <100 mg/dL (2.59 mmol/L) (primary prevention) in the anacetrapib 100 mg group relative to placebo after 52 weeks of treatment.
3. Evaluate the proportion of patients achieving >=50% reduction from baseline LDL-C in the anacetrapib 100 mg group relative to placebo after 52 weeks of treatment.
4. Evaluate the lipid-modifying efficacy of anacetrapib (100 mg) added to

different background statins (e.g. simvastatin, atorvastatin, rosuvastatin) compared to placebo after 52 weeks of treatment.
5. Evaluate the effect of anacetrapib (100 mg) on CETP concentration and activity compared to placebo after 52 weeks of treatment.
6. Evaluate the effect of anacetrapib (100 mg) compared to placebo after 52 weeks of treatment on lipid endpoints as per patient's molecular diagnosis of HeFH.
7. Compare the effect of anacetrapib (100 mg) on LDL-C measured by different methods (i.e. direct, Friedewald and beta-quantification) after 52 weeks of treatment.
8. To evaluate the duration of dosing on the elimination kinetics of anacetrapib

Study design

This is a multicenter, double-blind, randomized, placebo-controlled study of 52 weeks duration in patients with HeFH who have been treated with an optimal dose of statin with or without other lipid-modifying agents (e.g. ezetimibe, niacin, fibrate). After a screening period and a 2-week placebo run-in period, 300 eligible patients on statins + other lipid-modifying therapies will be randomized to either anacetrapib 100 mg or placebo in a 2:1 ratio for 1 year. As shown in the Study Flow Chart, the study includes 8 scheduled clinic visits during the 52-week treatment period. One post-study follow-up visit will occur 12 weeks after early discontinuation or completion of the study drug treatment to query for adverse experiences. All patients discontinuing will also be contacted at their intended Week 52 (Visit 8) date to assess for serious cardiovascular adverse events or death.
Women of child-bearing potential when discontinued, patients are contacted by phone at their intended Week 52 (visit 8) date or their intended Week 64 (visit 9) date and recommended to use acceptable contraception during the 4 year time period after stopping the study drug. Pregnancy will be reported to the Sponsor to 4 years of completing the study. Women of child-bearing potential will be contacted annually by telephone until 4 years after treatment stop, to question about a possible pregnancy.
Consistent with the adjudication SOP, selected adverse cardiovascular events and all-cause mortality will be adjudicated by an expert committee independent of the SPONSOR.

Intervention

After randomization patient s will receive during 52 weeks together with the standard therapy, a daily dose of Anacetrapib of 100 mg/day or a matching placebo.
The clinical safety will be evaluated during every visit.
Controles can be physical examination, measurement of the vital signs and clinical lab measurements, such as lipid tests, biomarkers for cardiovascular

risk and lab tests of safety.
All patients will undergo an ECG at visit 2 and 8.

Study burden and risks

For all details refer to the the study flow chart on page 11-13 of the protocol.
Also refer to E4, E6 and E9 for burden and possible risks.

Contacts

Public
Merck Sharp & Dohme (MSD)

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Scientific
Merck Sharp & Dohme (MSD)

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Kenilworth NJ 07033
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Patient is male or female and >=18 and <=80 years of age on day of signing informed consent.

- A female patient who is of reproductive potential agrees to remain abstinent* or use (or have their partner use) 2 acceptable methods of birth control for the duration of the study. Acceptable methods of birth control are: intrauterine device (IUD), diaphragm with spermicide, condom, vasectomy and hormonal contraception. (A female patient who is NOT of reproductive potential is eligible without requiring the use of contraception.)
- Patient has been diagnosed with HeFH defined as:
• Documentation of known mutation in a copy of the patient*s LDL receptor, Apo B, or PCSK9 genes OR
In the absence of a genetic diagnosis, a patient must have a documented history of one or more of the following:
• Documented history of untreated TC >290 mg/dL (7.5 mmol/L) OR
• untreated LDL-C >190 mg/dL (4.9 mmol/L)
AND at least ONE of the following:
• Documented history or presence of a tendinous or cutaneous xanthoma in the patient or a first-degree relative
• Documented history or presence of a mutated copy of the LDL receptor or apo B gene in an adult first-degree relative or biological offspring
• Documented history in a first-degree adult relative with untreated TC >350 mg/dL (9.1 mmol/L) or untreated LDL-C >190 mg/dL (4.9 mmol/L)
• Documented history in a first degree relative <18 years of age with untreated TC >280 mg/dL (7.2 mmol/L) or LDL-C >160 mg/dL (4.1 mmol/L)
• Documented history in a first degree relative of premature coronary artery disease or sudden death from natural causes prior to age 55 years if male or prior to age 60 years if female
- LDL-C >100 mg/dL (2.59 mmol/L) without documented history of CVD or LDL-C >70 mg/dL (1.81 mmol/L) with documented history of CVD
- c. Patients have been treated with an optimal dose of statin (i.e. one of the following) for at least 6 weeks prior to Visit 1:
• simvastatin 40 mg or 80 mg
• atorvastatin 20 mg, 40 mg or 80 mg
• rosuvastatin 5 mg, 10 mg, 20 mg or 40 mg
• pitavastatin 4 mg
• lovastatin 80 mg
• pravastatin 80 mg
- Patient has a TG <400 mg/dL (4.52 mmol/L).
- Patient has creatine phosphokinase (CPK) <=2 x upper limit of normal (ULN) [per central laboratory reference ranges].
- Patient has alanine aminotransferase (ALT) or aspartate aminotransferase (AST) <=2 x upper limit of normal (ULN) [per central laboratory reference ranges].
- Subjects provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
- Patient is greater than 75% compliant with study medication during the single-blind placebo run-in phase or in the opinion of the investigator, compliance will improve following additional counseling.

Exclusion criteria

- Patient received treatment with LDL apheresis within 4 weeks of Visit 1 or expected to undergo treatment with LDL aphresis during the course of the study.
- Patient has homozygous familial hypercholesterolemia.
- Patient has severe chronic heart failure defined by New York Heart Association (NYHA) Classes III or IV.
- Patient has uncontrolled cardiac arrhythmias, MI, PCI, CABG, unstable angina, or stroke within 3 months prior to Visit 1.
- Patient has uncontrolled hypertension (for definition refer to protocol synopis p.10)
- Patient has uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins (i.e., secondary causes of hyperlipidemia).
- Patient has active or chronic hepatobiliary, hepatic or gall bladder disease.
- Patient has eGFR <30 mL/min/1.73m2 based on 4-variable MDRD (Modification of Diet in Renal Disease) equation, nephrotic syndrome or other clinically significant renal disease.
- Patient has history of mental instability, drug/alcohol abuse within the past 5 years or major psychiatric illness inadequately controlled and unstable.
- Patient is pregnant or breast-feeding, or plans to become pregnant during the study or after stopping study medication.
- Patient has history of ileal bypass, gastric bypass, or other significant condition associated with malabsorption.
- Patient is human immunodeficiency virus (HIV) positive (as assessed by medical history).
- Patient has a history of malignancy <=5 years prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
- Patient has donated blood products or has had phlebotomy of >300 mL within 8 weeks of signing informed consent, or intends to donate 250 mL of blood products or receive blood products within the projected duration of the study.
- Patient has a history or current evidence of any condition, therapy, lab abnormality or other circumstance that might confound the results of the study, or interfere with the patient's participation for the full duration of the study, such that it is not in the best interest of the patient to participate.

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):	10-02-2012
Enrollment:	120
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Niet beschikbaar
Generic name:	Anacetrabip

Ethics review

Approved WMO Date:	15-12-2011
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-01-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-03-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-03-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	22-03-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-04-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-05-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-05-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-11-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-12-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-02-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-04-2013

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-04-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-11-2013
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:	19-02-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-01-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	15-08-2016
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	EUCTR2011-004525-27-NL
CCMO	NL38480.056.11