A 24-Week, 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 Hypercholesterolemia or Low HDL-C

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Primary Objectives:1. To evaluate the efficacy of anacetrapib 100 mg for 24 weeks relative to placeboon plasma concentrations of LDL-C (BQ method).2. To evaluate the efficacy of anacetrapib 100 mg for 24 weeks relative to placeboon plasma…

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

Summary

ID

NL-OMON40028

Source
ToetsingOnline

Brief title
MK-0859-021

Condition

- Lipid metabolism disorders

Synonym
high cholesterol levels

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Anacetrapib, Hypercholesterolemia, Placebo, Statin Therapy

Outcome measures

Primary outcome

The co-primary efficacy endpoints are the percent change from baseline in LDL-C

(BQ

method) and HDL-C at Week 24. Non-HDL-C, apoB, apoA-I, Lp(a) at Week 24 and

HDL-C at Week 24 among patients with low HDL-C at LDL-C goal are efficacy

variables addressing the secondary hypotheses.

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

Some other endpoints of interest are percent change from baseline at Week 24

are TC, TG, apoE, VLDL-C, VLDL-TG, LDLC/HDL-C, apoB/apoA-I, LDL-C/apoB,

TC/HDL-C, LDL-C estimated by direct and Friedewald methods, CETP activity and

CETP concentration.

Study description

Background summary

This study supports the use of anacetrapib as an add-on to statin therapy with or without other lipid-modifying medication(s) in high, moderate and low CHD-risk patients with hypercholesterolemia who are not at LDL-C goal (as per NCEP ATP III guidelines) and in patients with low HDL-C who are at LDL-C goal. Moreover, since patients will be allowed to enter the study on a high efficacy statin ± other lipid-modifying therapies, the data will be used to support the use of anacetrapib with any high efficacy dose of commonly used statins or with ezetimibe, niacin or fibrates + statin. Additionally, this study will provide efficacy and tolerability data for a lower (25 mg) dose of anacetrapib.

Study objective

Primary Objectives:
1. To evaluate the efficacy of anacetrapib 100 mg for 24 weeks relative to placebo on plasma concentrations of LDL-C (BQ method).
2. To evaluate the efficacy of anacetrapib 100 mg for 24 weeks relative to placebo on plasma concentrations of HDL-C.
3. To evaluate the safety and tolerability of anacetrapib 100 mg for 24 weeks.

Hypotheses;
1. Treatment with anacetrapib 100 mg for 24 weeks will lower LDL-C (BQ method) to a greater extent than treatment with placebo.
2. Treatment with anacetrapib 100 mg for 24 weeks will raise HDL-C to a greater extent than treatment with placebo.

Secondary Objectives:
1. To evaluate the efficacy of adding anacetrapib 100mg for 24 weeks relative to

placebo on plasma concentrations of non-HDL-C.
2. To evaluate the efficacy of adding anacetrapib 100mg for 24 weeks relative to placebo on plasma concentrations of apoB.
3. To evaluate the efficacy of adding anacetrapib 100mg for 24 weeks relative to placebo on plasma concentrations of apoA-1.
4. To evaluate the efficacy of adding anacetrapib 100mg for 24 weeks relative to placebo on plasma concentrations of Lp(a).
5. To evaluate the effect of anacetrapib 100 mg on HDL-C in patients with low HDL-C at LDL-C goal after 24 weeks of treatment.
6. To evaluate the LDL-C-decreasing efficacy of anacetrapib 25 mg vs. placebo after
24 weeks of treatment.
7. To evaluate the HDL-C-increasing efficacy of anacetrapib 25 mg vs. placebo after
24 weeks of treatment.
8. To evaluate the efficacy of adding anacetrapib 25mg for 24 weeks relative to placebo on plasma concentrations of non-HDL-C.
9. To evaluate the efficacy of adding anacetrapib 25mg for 24 weeks relative to placebo on plasma concentrations of apoB.
10. To evaluate the efficacy of adding anacetrapib 25mg for 24 weeks relative to placebo on plasma concentrations of apoA-1.
11. To evaluate the efficacy of adding anacetrapib 25mg for 24 weeks relative to placebo on plasma concentrations of Lp(a).
12. To evaluate the effect of anacetrapib 25 mg on HDL-C in patients with low HDLC
at LDL-C goal after 24 weeks of treatment.
13. To evaluate the safety and tolerability of anacetrapib 25 mg for 24 weeks.

Hypotheses:
1. Treatment with anacetrapib 100mg for 24 weeks will lower non-HDL-C to a greater extent than treatment with placebo.
2. Treatment with anacetrapib 100mg for 24 weeks will lower apoB to a greater extent than treatment with placebo.
3. Treatment with anacetrapib 100mg for 24weeks will raise apoA-1 to a greater extent than treatment with placebo.
4. Treatment with anacetrapib 100mg for 24 weeks will lower Lp(a) to a greater extent than treatment with placebo.
5. Treatment with anacetrapib 100 mg for 24 weeks in patients with low HDL-C at LDL-C goal will raise HDL-C to a greater extent than treatment with placebo.
6. Treatment with anacetrapib 25 mg for 24 weeks will lower LDL-C to a greater extent than treatment with placebo.
7. Treatment with anacetrapib 25 mg for 24 weeks will raise HDL-C to a greater extent than treatment with placebo.
8. Treatment with anacetrapib 25mg for 24 weeks will lower non-HDL-C to a greater extent than treatment with placebo.
9. Treatment with anacetrapib 25mg for 24 weeks will lower apoB to a greater extent than treatment with placebo.

10. Treatment with anacetrapib 25mg for 24 weeks will raise apoA-1 to a greater extent than treatment with placebo.
11. Treatment with anacetrapib 25mg for 24 weeks will lower Lp(a)to a greater extent
than treatment with placebo.
12. Treatment with anacetrapib 25 mg for 24 weeks in patients with low HDL-C at LDL-C goal will raise HDL-C to a greater extent than treatment with placebo.
Exploratory
1. To evaluate the LDL-C-decreasing efficacy of anacetrapib 100 mg vs. 25 mg after
24 weeks of treatment.
2. To evaluate the HDL-C-increasing efficacy of anacetrapib 100 mg vs. 25 mg after
24 weeks of treatment.
3. To evaluate the proportion of patients reaching LDL-C goal relative to placebo
after 24 weeks of treatment in patients not at LDL-C goal at baseline.
4. To evaluate the lipid-modifying efficacy of anacetrapib (25mg, 100mg) added to
different background statins (i.e. simvastatin, atorvastatin, rosuvastatin) with or
without other LMTs compared to placebo after 24 weeks of treatment.
5. To evaluate the effects of anacetrapib (25mg, 100 mg) relative to placebo on TG,
TC, TC/HDL-C, LDL-C/HDL-C, apoB/apoA-I, LDL-C/apoB, apoE, VLDL-C,
VLDL-TG, CETP activity and CETP concentration after 24 weeks of treatment.
6. To evaluate the proportion of patients reaching HDL-C >=*60mg/dL (1.55 mmol/L) relative to placebo after 24 weeks of treatment with anacetrapib (100mg, 25mg) in
patients with HDL below 40 mg/dL (1.03 mmol/L) at baseline.
7. To evaluate the LDL-C lowering and HDL-C raising effect of anacetrapib by baseline CETP activity and CETP concentration.
8. To evaluate the effects of anacetrapib (25mg, 100mg) on lipid endpoints in patients with diabetes after 24 weeks of treatment.
9. To evaluate the effect of anacetrapib (25mg, 100mg) on fasting plasma glucose,
fasting plasma insulin, HbA1c and HOMA-IR (homeostatic model assessment of insulin resistance) after 24 weeks of treatment.
10. To evaluate the effects of cessation of anacetrapib (25mg, 100mg) for 12 weeks
on lipid endpoints and PK.
11. To evaluate the safety and tolerability of anacetrapib (25mg, 100mg) 12 weeks
after cessation of treatment.

Study design

This is a multicenter, double-blind, placebo-controlled study in patients with hypercholesterolemia or low HDL-C on a stable dose of statin ± other lipid-modifying
therapies (LMTs) e.g. ezetimibe, niacin, fibrate.
Patients should be on treatment with a stable dose-regimen of statin ± other lipidmodifying
therapies for at least 6 weeks prior to Visit 1, and are required to remain on the
same regimen for the duration of the study. Approximately 450 patients will be randomized in a 1:1:1 ratio to treatment with anacetrapib 100 mg, anacetrapib 25 mg or
placebo for 24 weeks.
As shown in the study flow chart the total duration of the study will be 40 weeks; which
will include a 2-week screening period (visits 1 to 2), 2-week placebo run-in period
(visits 2 to 3) and a 24-week treatment period (visits 3-6), followed by a post-study
follow-up visit 12 weeks after early discontinuation or completion of study drug treatment. All patients discontinuing will also be contacted at their intended Week 36
date to assess for serious cardiovascular adverse events, all-cause death or pregnancy in
women of child-bearing potential.
Consistent with the adjudication SOP, selected adverse cardiovascular events and allcause
mortality will be adjudicated by an expert committee independent of the SPONSOR.

Intervention

Patients will take once a day two tablets during the meal. Patients will take daily one tablet of anacetrapib 100 mg or corresponding placebo and one tablet of anacetrapib 25 mg or corresponding placebo for 24 weeks.
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.

Study burden and risks

Please refer to the details of the study flowchart on page 11 to 13 of the protocol. See also section E4, E6 and E9 for risks and burden.

Contacts

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US
Scientific
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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

Patients will be eligible to continue to Visit 2 if they meet the following criteria at Visit 1:
1. Patient is male or female and >=18 and <=80 (or maximum age less than 80; per local regulation) years of age on day of signing informed consent.
2. A female patient should NOT be of reproductive potential. A female patient not of reproductive potential is defined as: one who has either 1) reached natural menopause defined as age 46 or older with a) 12 months of spontaneous amenorrhea or b) 6 months of spontaneous amenorrhea with serum FSH levels in the postmenopausal range as determined by the central laboratory, 2) 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, or 3) bilateral tubal ligation.
3. Patient is not pregnant or breast-feeding and does not plan to become pregnant any time in the future.

4. As per NCEP ATP III CHD risk category at screening, patients are required to meet ONE of the following criteria (detailed definitions of risk categories are in Appendix 6.7):
a. Very high risk patients (presence of established CHD or other forms of atherosclerotic vascular disease plus multiple major risk factors [e.g. diabetes], severe and poorly controlled risk factors [e.g. cigarette smoking], multiple risk factors of the metabolic syndrome [e.g. high triglycerides >=200mg/dL (2.26 mmol/L) plus non-HDL-C >=130 mg/dL (3.36 mmol/L) with low HDL-C <40mg/dL (1.03 mmol/L)] or acute coronary syndrome.) with LDL-C >=70 to <115 mg/dL (>=1.81 to <2.97 mmol/L)
b. High risk patients (CHD or CHD risk equivalent, DM, 10-yr risk>20%) with LDL-C >=100 to <145 mg/dL (>=2.59 to <3.75 mmol/L);c. Moderate risk patients(>=2 risk factors; 10-yr risk <=20%) with LDL-C >= 130 mg/dL (>= 3.36 mmol/L)
d. Lower risk patients (0 to 1 risk factor) with LDL-C >= 160 mg/dL (>=4.14 mmol/L)
e. Patients at LDL-C goal (as per CHD- risk category) and with low HDL-C, <40 mg/dL (1.03 mmol/L)
5. Patient has been treated with an appropriate dose of statin as assessed by the investigator (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
Note: Lipid modifying therapy must be stable for at least 6 weeks prior to Visit 1. Patients are expected to take statin under supervision of their treating physician in accordance with statin product circular in that region.
6. Patients provide written informed consent/assent for the trial. The patient may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
Note: Patient with laboratory values outside ranges described in the protocol may, at the discretion of the investigator, have ONLY ONE repeat determination performed and if the repeat value satisfies the criterion patient may continue.
Visit 3
Patients are eligible for randomization if they meet the following criteria at Visit 3.
7. 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

Visit 1
1. Patient has previously participated in a study with a CETP inhibitor.
2. Patient has homozygous familial hypercholesterolemia.

3. Patient has a TG > 600 mg/dL (6.78 mmol/L)
4. Patient has creatine phosphokinase (CPK) >2 x upper limit of normal (ULN) [per central laboratory reference ranges].
5. Patient has alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 x upper limit of normal (ULN) [per central laboratory reference ranges].
6. Patient has severe chronic heart failure defined by New York Heart Association (NYHA) Classes III or IV.
7. Patient has uncontrolled cardiac arrhythmias, MI, PCI, CABG, unstable angina, or stroke within three months prior to Visit 1.
8. Patient has uncontrolled hypertension defined as follows:
Sitting diastolic blood pressure >=100 mmHg, or sitting systolic blood pressure >=160 mm Hg (non-diabetic patients).
OR
Sitting diastolic blood pressure >=90 mmHg, or sitting systolic blood pressure >=150 mm Hg (diabetic patients).
9. Patient has uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins (i.e., secondary causes of hyperlipidemia).
Note: Patients with thyroid stimulating hormone (TSH) values outside the central laboratory normal range who are determined to be without symptoms of either hypo- or hyperthyroidism may be allowed in the study if, after review by the Investigator and Project Physician, the patient is deemed not to have clinically significant thyroid hormone excess or deficiency.
10. Patient has active or chronic hepatobiliary, hepatic or gall bladder disease. Note: Patients with chronic hepatitis B or C or non-alcoholic steatosis are allowed in the study if ALT and AST are within protocol-specified range
11. Patient has eGFR <30 mL/min/1.73m2 based on the 4-variable MDRD (Modification of Diet in Renal Disease) equation, nephrotic syndrome or other clinically significant renal disease.
12. Patient has history of mental instability, drug/alcohol abuse within the past five years or major psychiatric illness inadequately controlled and unstable.
13. Patient has history of ileal bypass, gastric bypass, or other significant condition associated with malabsorption.
14. Patient is human immunodeficiency virus (HIV) positive (as assessed by medical history).
15. 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.
16. Patient has donated blood products or has had phlebotomy of >300 mL within eight 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.
17. 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.
18. Patient is currently taking medications that are potent inhibitors or inducers of CYP3A4 (including but not limited to cyclosporine, systemic itraconazole or ketoconazole, erythromycin, clarithromycin, or telithromycin, nefazodone,

protease inhibitors, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St John*s wort) or has discontinued treatment <3 weeks prior to Visit 1. Consumption of >1 liter of grapefruit juice per/day is also prohibited.
19. Patient is currently participating or has participated in a study with an investigational compound or device within three months of signing informed consent.
20. Patient consumes more than two alcoholic drinks per day.
21. Patient is receiving treatment with systemic corticosteroids.
Note: Treatment with corticosteroids used as replacement therapy for pituitary/adrenal disease is acceptable; however, the patient must have been on a stable regimen for at least six weeks prior to Visit 1.
22. Patient is taking systemic anabolic agents.
Additional details regarding excluded concomitant medications can be found in Appendix 6.10.
Note: Patient with laboratory values outside ranges described in the protocol may, at the discretion of the investigator, have ONLY ONE repeat determination performed and if the repeat value satisfies the criterion patient may continue.

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):	03-06-2013
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Not Applicable
Generic name:	Anacetrapib

Ethics review

Approved WMO Date:	17-10-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-12-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-02-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-11-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-11-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	14-11-2014
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	EUCTR2012-003110-14-NL
CCMO	NL42135.056.12