A Phase 3b, Multi-Center, Double-Blind, Placebo-Controlled, Parallel Group, Study to Evaluate the Effect of Dalcetrapib 600 mg on Cardiovascular (CV) Events in Adult Patients with Stable Coronary Heart Disease (CHD), CHD Risk Equivalents or at Elevated Risk for Cardiovascular Disease (CVD).

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Ethical review	Approved WMO
Status	Pending
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON37839

Source
ToetsingOnline

Brief title
dal-OUTCOMES 2

Condition

- Coronary artery disorders

Synonym
Cardiovascular disease, Coronary Heart Disease

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: Pharmaceutical industry: Hoffman- La Roche

Intervention

Keyword: Cardiovascular Events, dalcetrapib, double-blind, Phase 3b

Outcome measures

Primary outcome

The primary endpoint of this study is the time to first occurrence of any

component of the composite endpoint; including

• Coronary heart disease death

• Non-fatal MI

• Fatal and non-fatal stroke of ischemic origin

Secondary outcome

The secondary endpoints of this study are listed below.

Time to first occurrence of:

• A composite including coronary heart disease death, nonfatal MI, fatal and

non-fatal stroke of ischemic origin and coronary revascularization

• A composite including coronary heart disease death, nonfatal MI, fatal and

non-fatal stroke of ischemic origin and hospitalization for unstable angina

• A composite including cardiovascular death, non-fatal MI and non-fatal stroke

• All-cause mortality

• A composite including all-cause mortality, non-fatal MI, non-fatal stroke

• Individual components of the primary endpoint

• Coronary revascularization, i.e. PCI or CABG; including separate analysis for

PCI and CABG

• Hospitalization for unstable angina

Percent change from baseline for:

• Blood lipid markers (TC, TG, HDL-C, LDL-C, Apo A1, ApoB)

• Biomarkers of CV risk

Study description

Background summary

Cardiovascular disease (CVD) is a major cause of premature death worldwide and an important source of disability, contributing in large part to the escalating costs of health care.
Along with many other factors, decreased high density lipoprotein cholesterol (HDL-C) levels have been linked to an increased risk of developing coronary heart disease (CHD) and have been given increased attention as a focus for treatment.
Dalcetrapib is a compound selected for its capacity to modulate plasma CETP activity and increase HDL-C levels. The currently ongoing phase 3 cardiovascular morbidity and mortality study dal-OUTCOMES targets a very high risk patient population (patients recently hospitalized for ACS but in stable condition). However, it has been identified that there is also an unmet need for effective interventions capable of reducing residual cardiovascular risk and microvascular complications in a patient population of slightly lower risk as compared to the dal-OUTCOMES patient population. Therefore, in this dal-OUTCOMES 2 study, the sponsor evaluates the potential of dalcetrapib (in addition to background therapy for other risk factors) to reduce cardiovascular morbidity and mortality in adult patients with stable CHD, CHD risk equivalents or at elevated risk for CV mortality and morbidity on the basis of multiple risk factors for CVD by raising HDL-C.

Study objective

The objectives of this study are:
- to evaluate the potential of dalcetrapib to reduce cardiovascular morbidity and mortality in adult patients with stable coronary heart disease (CHD), CHD risk equivalents or at elevated risk for cardiovascular disease (CVD).

- to assess the long term safety and tolerability of dalcetrapib

- to evaluate the effect of dalcetrapib on lipid markers and biomarkers of CV risk.

Study design

This study will be a randomized, double-blind, placebocontrolled, parallel group, multi-center study in adult patients with stable coronary heart disease (CHD), CHD risk equivalents or at elevated risk for cardiovascular disease (CVD).

Eligible patients will be randomized in a 1:1 ratio to 600 mg dalcetrapib or matching placebo. Patients will receive dalcetrapib on a background of contemporary, guidelines-based medical care for patients with stable coronary heart disease (CHD), CHD risk equivalents or at elevated risk for cardiovascular disease (CVD).
Patients will visit the clinic 1 and 6 months after randomization and every 6 months thereafter until completion of the trial. Patients will be contacted by phone 3 months after randomization. Patients prematurely and permanently discontinuing study treatment will be followed-up by adhering to the visit schedule or will be contacted by phone every 6 months until the end of the study to assess occurrence of CV events/vital status.

The trial will last until approximately 1,250 patients are anticipated to have experienced a primary endpoint event. This is anticipated to occur approximately 4 to 5 years after the first patient is randomized. A phone safety follow-up visit will be performed 4 weeks after the end of treatment visit.

Three interim analyses of efficacy will be conducted when approximately 600, 850 and 1050 patients are anticipated to have experienced a primary endpoint event that has been positively adjudicated.

Intervention

Patients will be subjected to the following interventions/procedures or defined behavioural rules:
-patients will be asked about personal data (age, race and gender), medical history, medical problems and which medicines they take.
-pregnancy test (blood or urine)

-blood pressure, heart rate, weight, height and circumference measurements
-physical examination
-blood draws, for some of which the patient has to come fasting
-phone calls to determine how the patient is doing and if he/she has had any medical problems.
-patients will be asked to take two tablets orally at approximately the same time every day during or immediately following a meal.
-female patients must use appropriate birth control

Study burden and risks

Patients may have side effects from the dalcetrapib or the procedures used in this study, some of which may not yet be known.

So far about 1000 healthy volunteers and about 1400 patients have received dalcetrapib in several completed studies. About 17,000 patients are currently participating in studies with dalcetrapib, 600 mg per day.
The most common side effect in these previous studies was:
•Diarrhea and stool abnormalities (10-15%)

Other common (1-10%) side effects included:
•dizziness
•headache

Of all these side effects, only diarrhea is considered to be caused by dalcetrapib.

Treatment with dalcetrapib may improve blood levels for HDL-C. Data from population studies, clinical trials with other HDL-C increasing compounds as well as data from animal studies, suggest that increasing HDL-C could reduce future cardiovascular risk.
Furthermore, the close medical attention the patient gets during the study may result in him/her gaining new information about his/her health which may provide benefits for his/her general health and well-being.
However, it is still possible that the patient will not have any benefit from participating in this research.

Please see protocol section 1.2.2 for more details about the anticipated risks and benefits of participation in this study.

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

1. Male and female patients at least 45 years of age with stable CHD, CHD risk equivalents or at elevated risk for CVD defined as the documented presence of at least one criterion in the categories A to D or at least 3 criteria in category E:;Patients with established CVD:;A. Stable coronary heart disease (CHD):
• Prior myocardial infarction (> 3 months prior to randomization)
• Prior coronary revascularization (PCI or CABG) (> 3 months prior to randomization)
• Angiographic or CT-imaging (e.g., MDCT/CTA) evidence of coronary atherosclerosis (> 70% stenosis in at least one major epicardial coronary artery);B. Cerebrovascular disease:
• Prior ischemic stroke (> 3 months prior to randomization) confirmed by a brain imaging study -
CT or MRI; thought not to be caused by atrial fibrillation, valvular heart disease or mural thrombus
• Carotid artery stenosis > 70% on prior angiography or ultrasound
• History of prior percutaneous or surgical carotid artery revascularization (> 3 months prior to randomization);C. Peripheral arterial disease (PAD):
• Prior documentation of a resting ankle-brachial index <= 0.85
• History of prior percutaneous or surgical revascularization of an iliac, femoral, or popliteal artery

(> 3 months prior to randomization)
• Prior non-traumatic amputation of a lower extremity (> 3 months prior to randomization) due to peripheral artery disease;Patients without established CVD:;D. Patients with pharmacologically treated type 2 diabetes and one or more additional risk factor for CVD:
• Age at least 70 years
• History of type 2 diabetes at least15 years
• eGFR at least 30 and max 60 ml/min/1.73m2 using the MDRD formula within 1 year prior to randomization
• Albuminuria defined as spot urine albumin to creatinine ratio (ACR) at least 30 µg albumin /mg creatinine within 1 year prior to randomization;E. Patients with 3 or more of the following risk factors for CVD but without T2D:
• HDL-C < 40 mg/dL (1.03 mmol/L) for men; < 50 mg/dL (1.29 mmol/L) for women within 1 year prior to randomization
• Waist circumference at least 94 cm (men) at least 80 cm (women); at least 90 cm (men) at least 80 cm (women) for Asians and patients of Asian descent within 1 year prior to randomization
• Hypertension: persistent elevated SBP at least 140 mmHG and/or DBP at least 90 mmHG despite treatment for hypertension
• Family history of premature CHD (symptomatic CHD in male first degree relative < 55 years or in female first degree relative < 65 years. Symptomatic CHD defined as myocardial infarction or coronary revascularization)
• Albuminuria defined as spot urine albumin to creatinine ratio (ACR) at least 30 µg albumin /mg creatinine within 1 year prior to randomization
• eGFR at least 30 and max 60 ml/min/1.73m2 using the MDRD formula within 1 year prior to randomization
• Current cigarette smoking;Appropriate documentation may include mention of the diagnosis in a discharge letter or in the patient*s file.;2. Within 6 months prior to randomization, evidence of guidelines-based management of LDL-C, at a minimum to include medical and dietary treatment to a level of LDL-C <100 mg/dL (2.6 mmol/L). Patients may be randomized if they cannot reach the goal of LDL-C < 100 mg/dL despite an intensive statin / LDL-C lowering drug regimen (comprising of a maximum tolerated dose of statin as determined by the investigator) or are unable to tolerate statins. For very-high risk patients (e.g. patients with a recent myocardial infarction, patients with cardiovascular disease combined with diabetes or metabolic syndrome or severe/poorly controlled risk factors), there is a therapeutic option to treat to a level of LDL-C < 70 mg/dL. In addition, if future or updated national or international guidelines recommend different LDL-C goals, LDL-C lowering medications should be adjusted accordingly to achieve these goals where possible.;3. Signed informed consent obtained prior to any study specific procedures.

Exclusion criteria

1. Occurrence of myocardial infarction, hospitalization for unstable angina, stroke or revascularization (coronary, carotid or peripheral) within three months prior to randomization.

2. Planned revascularization (coronary, carotid or peripheral) after randomization.
3. Sustained systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg.
4. Symptomatic congestive heart failure (NYHA Class III or IV).
5. Known left ventricular ejection fraction < 25%.
6. Presence of any of the following laboratory abnormality assessed within 6 months prior to randomization:
a. Triglycerides at least 400 mg/dL (4.5 mmol/L),
b. Hepatic transaminase > 2 x ULN or alkaline phosphatase levels > 2 x ULN or total bilirubin level > 1.5 x ULN
c. Creatine phosphokinase levels > 3 x ULN
d. eGFR < 30 ml/min/1.73m2 using the MDRD formula
e. or any laboratory abnormality that is considered to be clinically important by the investigator.
7. Known HbA1c > 10%
8. Known Hb < 8 g/dL
9. Current or previous (within 3 months prior to randomization) treatment with niacin, fibrates, bile acid sequestrants or drugs other than dalcetrapib administered for increasing HDL-C (treatment with ezetimibe, fish oil derivatives and multivitamins containing nicotinic acid (vitamin B3) is permitted).
10. Previous treatment with compounds targeting CETP, e.g. torcetrapib, anacetrapib or dalcetrapib.
11. Known or suspected intolerance or hypersensitivity to lactose.
12. Patients with clinically apparent liver disease, eg, jaundice, cholestasis, or active hepatitis.
13. History of malignancy (except for curatively treated basal cell or squamous cell carcinoma of the skin) during the 3 years prior to randomization.
14. Any clinically significant medical condition that according to the investigator could interfere with the conduct of the study or life expectancy shorter than the duration of the trial.
15. Current alcohol or drug abuse or history thereof within 5 years prior to randomization.
16. Patients who have received any investigational drug or device within 1 month prior to randomization, or who are expected to participate in any other investigational drug or device study during the conduct of this trial.
17. Women who are pregnant or breast-feeding.
18. Women of childbearing potential who are not using a highly effective contraceptive method at randomization (see protocol section 4.2.2).
19. Unable or unwilling to comply with protocol requirements throughout the duration of the trial (approximately 4 to 5 years follow-up), or deemed by the investigator to be unfit for the study.

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:	Prevention

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2012
Enrollment:	740
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	dalcetrapib

Ethics review

Approved WMO Date:	20-12-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-02-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-03-2012

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-03-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-03-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-03-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-03-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-04-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-05-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2011-001891-21-NL
ClinicalTrials.gov	NCT01516541
CCMO	NL38771.060.11