A phase III, double-blind, randomized placebo-controlled study to evaluate the effects of dacetrapib on cardiovascular (CV) risk in a genetically defined population with a recent Acute Coronary Syndrome (ACS): The dal-GenE trial

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Ethical review	Approved WMO
Status	Completed
Health condition type	Myocardial disorders
Study type	Interventional

Summary

ID

NL-OMON55786

Source
ToetsingOnline

Brief title
dal-GenE

Condition

- Myocardial disorders

Synonym
Acute Coronary syndrome, arterial disease

Research involving

Human

Sponsors and support

Primary sponsor: DalCor Pharma UK Ltd
Source(s) of monetary or material Support: Dalcor Pharma UK Ltd.

Intervention

Keyword: Acute Coronary Syndrome, Cardiovascular risk

Outcome measures

Primary outcome

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

component of the composite endpoint, as adjudicated by the Clinical Endpoint

Committee. Components of the primary endpoint are:

_Cardiovascular (CV) death

_Resuscitated cardiac arrest

_Non-fatal MI

_Non-fatal stroke

Secondary outcome

The key secondary endpoints of this study:

Time to first occurrence of:

_The composite of CV death, resuscitated cardiac arrest, non-fatal MI,

non-fatal stroke, or hospitalization for ACS (with ECG abnormalities) requiring

coronary revascularization

_The composite of CV death, resuscitated cardiac arrest, non-fatal MI,

non-fatal stroke, hospitalization for ACS (with ECG abnormalities), or

unanticipated coronary revascularization

_The composite of all cause death, resuscitated cardiac arrest, non-fatal MI,

or non-fatal stroke

Other secondary endpoints:

Time to first occurrence of:

_The composite of CV death, resuscitated cardiac arrest, non-fatal MI,

non-fatal stroke, or hospitalization for new or worsening heart failure

_The composite of CV death, resuscitated cardiac arrest, non-fatal MI,

non-fatal stroke, hospitalization for ACS (with ECG abnormalities) requiring

coronary revascularization, or hospitalization for new or worsening heart

failure

_The composite of all-cause death, resuscitated cardiac arrest, non-fatal MI,

non-fatal stroke, or hospitalization for new or worsening heart failure

_Fatal or non-fatal MI

_All-cause death

Study description

Background summary

Dalcetrapib is an investigational drug that has been evaluated in several large clinical trials, most notably dal-OUTCOMES, a study of over 15.000 patients which was designed to evaluate its effect in patients with recent ACS. The results of this large study demonstrated that treatment with dalcetrapib did not change the risk of cardiovascular disease in the majority of patients with recent ACS. However, after the study was over, researchers identified a group

of patients that had a significant benefit. The group of patients had a specific change in a gene. Patients who had the variant 'AA' of the ADCY9 gene had their risk of having another cardiovascular event reduced by 39%. Approximately 1 in 5 patients studied had this genetic variant. A different variant 'GG' found in roughly 2 in 5 patients was associated with a 27% increase in risk for a cardiovascular event in patients taking dalcetrapib. There was no difference in safety or tolerability between these groups.

The goal of the present study is to evaluate the effect of dalcetrapib in patients with the AA variant to confirm these findings of cardiovascular benefit.

Study objective

The primary objective of this trial is to evaluate the potential of dalcetrapib to reduce cardiovascular morbidity and mortality (cardiovascular death, resuscitated cardiac arrest, non-fatal myocardial infarction (MI) and non-fatal stroke) in subjects with a documented recent ACS and the AA genotype at variant rs1967309 in the ADCY9 gene.

Key secondary objectives of this trial:

Time to first occurrence of:
* The composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for ACS (with ECG abnormalities) requiring coronary revascularization
* the composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, hospitalization for ACS (with ECG abnormalities), or unanticipated coronary revascularization
* The composite of all cause death, resuscitated cardiac arrest, non-fatal MI, or non-fatal stroke

Other secondary objectives:
* assessment of the long-term safety profile of dalcetrapib in this population
*Evaluation of the effects of dalcetrapib on lipids and hsCRP in this population
*Evaluation of the effects of dalcetrapib on:
_The composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for new or worsening heart failure
_The composite of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, hospitalization for ACS (with ECG abnormalities) requiring coronary revascularization, or hospitalization for new or worsening heart failure
_The composite of all-cause death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or hospitalization for new or worsening heart failure
_Fatal or non-fatal MI
_All-cause death

Study design

This is a placebo-controlled, randomized, double-blind, parallel group, phase III multicenter study in subjects recently hospitalized for ACS and with the appropriate genetic profile. Subjects will provide informed consent before any study-specific procedures are performed. Subject enrollment may begin in the hospital and will continue following release from the hospital.
Screening procedures may be performed at the time of the index ACS event or anytime thereafter, with the confition that randomization must occur within the mandated window (4-12 weeks after the index event). Subjects will be assessed based on their medical history. those who are likely to qualify will undergo cobas® ADCY9 Genotype CTA (Clinical Trial Assay) testing to evaluate genetic determination for the presence of AA genotype at variant rs1967309 in the ADCY9 gene. Those meeting the genetic testing criteria, all other inclusion criteria, and non of the exclusion criteria will be eligible for randomization. Eligible subjects must be stabilized on statin and/or other medical therapy and have completed all planned revascularization procedures prior to randomization. Subjects must be randomized between 4 and 12 weeks after the index event. Eligible subjects in stable condition will be randomized to 600mg of dalcetrapib or placebo in a 1:1 ratio. Subjects will receive study medication or placebo on a background of contemporary, evidence-based medical care for ACS.

This is an event driven study and approximately 582 primary events are needed to reach 85% statistical power given all other assumptions. Subjects will visit the clinic 1 and 6 months after randomization. Thereafter visits will be approximately every 6 months for efficacy and safety assessments until completion of the trial. Phone assessments will be performed 3 months after randomization and at the end of the study. Additionally, for any subject prematurely discontinuing study medication, assessments will be conducted every 6 months for the collection of study endpoints and concomitant medication.

Intervention

Cohort A (n=3000): dalcetrapib 600mg
Cohort B (n=3000): placebo

Study burden and risks

Risks: possible side effects of the study medication

Burden: blood draws; fasting state before visits 2 and 5;

Contacts

Public
DalCor Pharma UK Ltd

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Zug CH-6302
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Scientific
DalCor Pharma UK Ltd

Stockport, Swiss Branch Zug, Baarerstrasse 2
Zug CH-6302
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects with the appropriate genetic background and recently hospitalized for ACS (between 1 and 3 months following the index event), will be enrolled in this trial. ACS is defined as the occurrence of at least one of the following events:
A) Myocardial Infarction (MI)
Spontaneous MI --> A diagnosis of a qualifying MI event will be defined by a rise and/or fall of cardiac biomarkers (preferably cardiac troponin) with at least one determination greater than the 99th percentile upper reference limit (URL) plus at least one of the following described below:
a. Symptoms of myocardial ischemia, or
b. New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block, or

c. Development of pathological Q waves in the ECG, or
d. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or
e. Identification of an intracoronary thrombus by angiography
Procedure-Related MI after Percutaneous Coronary Intervention (PCI) --> A procedure-related MI after PCI is defined as an increase of cardiac troponin values with at least one determination greater than 5 times the 99th percentile URL in patients with normal baseline values (less than or equal to 99th percentile URL) or a rise of cardiac troponin values > 20% if the baseline values are elevated and are stable or falling; plus at least one of the following described below:
a. Symptoms suggestive of myocardial ischemia
b. New ischemic ECG changes
c. Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality
d. Angiographic findings consistent with a procedural complication
B) Hospitalization for ACS (ECG Abnormalities without Biomarkers):
A diagnosis of a qualifying ACS event without increases in cardiac biomarkers will require admission to hospital or emergency room (exceeding 23hrs) with symptoms presumed to be caused by myocardial ischemia with an accelerating tempo in the prior 48hrs and/or prolonged (at least 20min) rest chest discomfort and new ECG findings (or presumed new if no prior ECG available) as described below and at least one of the following:
a. At least 50% stenosis of an epicardial coronary artery
b. Positive exercise or pharmacologic stress indicating reversible ischemia
c. Presence of pathologic Q-waves on ECG
In addition, the following inclusion criteria apply:
1. Both male and female subjects age 45 years and over at screening visit (V1)
2. Signed informed consent obtained prior to any study specific screening procedures
3. AA genotype at variant rs1967309 in the ADCY9 gene as determined by cobas® ADCY9 Genotype CTA testing, conducted at a designated investigational testing site (ITS)
4. Clinically stable, ie, free of ischemic symptoms at rest or with minimal exertion for at least 1 week prior to randomization
5. Prior to randomization, subject must have evidence of guidelines-based management of LDL-C, at a minimum to include medical and dietary treatment to a target level of LDL-C <100mg/dl (<2.6mmol/L). Subjects with an LDL-C level *100mg/dl (*2.6mmol/L) may be randomized if they cannot reach the target goal of less than 100mg/dl despite lipid-lowering regimen, or are unable to tolerate lipid-lowering regimen.

Exclusion criteria

1. Females who are pregnant (negative pregnancy test required for all women of

child-bearing potential at Visit 2, Day 0) or breast-feeding
2. Women of child-bearing potential (women who are not surgically sterile or postmenopausal defined as amenorrhea for >12 months) who are not using at least one method of contraception.
3. New York Heart Association (NYHA) Class III or IV heart failure
4. Last known hemoglobin <10g/dl
5. Index ACS event presumed due to uncontrolled hypertension
6. Systolic blood pressure (BP) >180mmHg and/or diastolic blood pressure >110mmHg by the time of randomization despite anti-hypertensive therapy
7. Last known serum triglyceride level >500mg/dl (>5.65mmol/L) as assessed within 6 months prior to randomization
8. Last known hemoglobin A1c (HbA1c) > 10% as assessed within 6 months prior to randomization
9. Subjects with clinically apparent liver disease, eg, jaundice, cholestasis, hepatic synthetic impairment, or active hepatitis
10. Last known ALT or AST level > 3 times the upper limit of normal (ULN) or last known alkaline phosphatase level > 2 times the ULN as assessed within 6 months prior to randomization (excluding index event)
11. History of persistent and unexplained creatine phosphokinase (CPK) levels > 3 times the ULN as assessed within 6 months prior to randomization (excluding index event)
12. Last known serum creatinine > 2.2mg/dl (195*mol/l) as assessed within 6 months prior to randomization
13. Previous exposure to anacetrapib or evacetrapib or documented allergic reaction to any CETP inhibitor
14. History of malignancy (except for curatively treated basal cell or squamous cell carcinoma of the skin) during the 1 year prior to the screening
15. Any clinically significant medical condition that according to the investigator could interfere with the conduct of the study
16. Subjects whose life expectancy is shorter than 3 years
17. Presence of any last known laboratory value as evaluated prior to randomization that is considered by the investigator to potentially limit the patient*s successful participation in the study
18. Current alcohol or drug abuse or history thereof within 2 years prior to screening that would likely interfere with compliance, based on investigator assessment
19. Subjects who have received any investigational drug within 1 month of randomization, or who expect to participate in any other investigational drug or device study during the conduct of this trial
20. Subjects unable or unwilling to comply with protocol requirements, or deemed by the investigator to be unfit for the study
21. Subjects who have undergone coronary artery bypass graft (CABG) surgery between the index event and randomization

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:	Completed
Start date (anticipated):	14-09-2016
Enrollment:	276
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	dalcetrapib
Generic name:	dalcetrapib

Ethics review

Approved WMO Date:	24-03-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	22-06-2016
Application type:	First submission

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	01-07-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	13-07-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	25-07-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	08-08-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	17-11-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	22-11-2016
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	06-12-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	30-01-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	15-03-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	16-03-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	27-10-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	28-11-2017
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	05-03-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	23-04-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	31-05-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	30-11-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	05-02-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	19-03-2019
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	01-06-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	01-07-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	02-07-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	02-04-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2015-003895-65-NL
CCMO	NL56500.098.16

Study results

Date completed: 11-05-2021

Results posted: 22-07-2022

Actual enrolment: 276

First publication
20-05-2022