Protocol I1V-MC-EIAN Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High-Risk for Vascular Outcomes - the ACCELERATE Study

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The primary objective of this study is to test the hypothesis that evacetrapib 130 mg daily, in comparison to placebo, reduces the incidence of the composite endpoint of cardiovascular (CV) death, myocardial infarction (MI), stroke, coronary...

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

Summary

ID

NL-OMON39898

Source
ToetsingOnline

Brief title
ACCELERATE

Condition

- Coronary artery disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Cardiovascular diseases, Heart- and vessel diseases

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly and Company
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: - Cardiovascular Events, - Cholesteryl Esther Transfer Protein (CETP), - High Risk Vascular Disease, - Lipid modification

Outcome measures

Primary outcome

Primary: Time to first occurrence of any component of the composite

cardiovascular (CV) events of death, myocardial infarction (MI), stroke,

coronary revascularization, or hospitalization for unstable angina (UA).

Secondary outcome

Secondary:

* Compared to placebo:

- Percent change from baseline of mean HDL-C levels at 3 months after

randomization

- Percent change from baseline of mean LDL-C levels at 3 months after

randomization

* Time to first occurrence of:

- A composite endpoint of all-cause mortality, MI, stroke, coronary

revascularization, or hospitalization for UA

- Composite endpoint of CV death, MI, or coronary revascularization

- Composite endpoint of CV death, MI, stroke, or hospitalization for UA

- Composite endpoint of CV death, MI, or stroke

* Time to first recurrence of:

- Any component of the primary composite endpoint among those who had already reached the primary endpoint

* Time to first occurrence of:

- Coronary revascularization

- MI

* Time to:

- CV death

- All-cause mortality

* Time to first occurrence of:

- Hospitalization for UA

- Stroke

Safety: Safety evaluations will be performed by recording treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and by monitoring laboratory parameters, physical examinations, ECGs and vital signs including systolic and diastolic blood pressure and pulse rate.

Besides that there are variables related to the tertiary, exploratory and

health economic objectives. Please see protocol chapter 10 for this.

Study description

Background summary

Evacetrapib (LY2484595) is a potent, selective inhibitor of cholesterol ester transfer protein (CETP) that has demonstrated ability to inhibit CETP activity, increase high-density lipoprotein cholesterol (HDL-C) and decrease low-density lipoprotein cholesterol (LDL-C).
Lipid modification, primarily through reduction in LDL-C by 3-hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), has been shown to reduce major adverse cardiovascular events (MACE) in a wide range of patients, including those with known coronary artery disease (CAD), as well as in patients with a history of acute coronary syndrome (ACS). Further lipid modification through adjunctive treatment with a CETP inhibitor may therefore similarly benefit a wide range of patients.
Epidemiologic data shows that higher levels of HDL-C and lower levels of LDL-C are associated with less atherosclerotic burden and lower risk for MACE. The pharmacodynamic (PD) effect of evacetrapib is expected to lead to a reduction in MACE in patients with vascular disease at high risk of subsequent cardiovascular events.
The PD effect of CETP inhibition has been tested in clinical trials with several CETP inhibitors, including torcetrapib (CP-529,414), anacetrapib (MK-0859), and dalcetrapib (JTT-705). Clinical trials clearly demonstrate CETP inhibition elevates HDL-C, and with more potent agents, lowers LDL-C; however, the hypothesis that lipid modulation by CETP inhibition will reduce the risk of cardiovascular events has yet to be confirmed in a clinical-outcome trial.
Patients for this Phase 3 study (Study I1V-MC-EIAN [ACCELERATE]) are those with known atherosclerotic vascular disease at high risk for subsequent cardiovascular events. The characteristics of these patients, termed high-risk vascular disease (HRVD), are patients with at least 1 of the following: 1) history of ACS (*30 days through 365 days after discharge for ACS); 2) cerebrovascular atherosclerotic disease; 3) peripheral arterial disease (PAD); or 4) diabetes mellitus (DM) with CAD.
Study EIAN (ACCELERATE) will evaluate the potential of evacetrapib to reduce MACE in patients with HRVD and will evaluate the efficacy and safety profile of evacetrapib.

Study objective

The primary objective of this study is to test the hypothesis that evacetrapib 130 mg daily, in comparison to placebo, reduces the incidence of the composite endpoint of cardiovascular (CV) death, myocardial infarction (MI), stroke, coronary revascularization, or hospitalization for unstable angina (UA) in high-risk vascular disease (HRVD) patients.

The secondary objectives of the study are to test the hypotheses that evacetrapib 130 mg daily, in HRVD patients
compared to placebo:
* Increases high-density lipoprotein-cholesterol (HDL-C) at 3 months after randomization
* Decreases low-density lipoprotein-cholesterol (LDL-C) at 3 months after randomization
Reduces the incidence of the following:
* A composite endpoint of all-cause mortality, MI, stroke, coronary revascularization, or hospitalization for
UA
* Composite endpoint of CV death, MI, or coronary revascularization
* Composite endpoint of CV death, MI, stroke, or hospitalization for UA
* Composite endpoint of CV death, MI, or stroke
* Recurrence of any component of the primary composite endpoint among those who had already reached
the primary endpoint
* Coronary revascularization
* MI
* CV death
* All-cause mortality
* Hospitalization for UA
* Stroke

Besides that there are tertiary, exploratory and health economic objectives. For further information, please see protocol chapter 6.

Study design

Study I1V-MC-EIAN (ACCELERATE) is a Phase 3, multicenter, randomized, parallel-group, double-blind, placebo-controlled, event-driven study with an estimated enrollment of 12,000 patients with HRVD.

Patients with HRVD are defined as patients with at least 1 of the following:
1) history of ACS (*30 days through 365 days after discharge for ACS);
2) cerebrovascular atherosclerotic disease;
3) peripheral arterial disease (PAD);
4) diabetes mellitus (DM) with coronary artery disease (CAD).

Eligible patients in stable condition (as judged by the responsible physician) and who meet all entry criteria will be randomized to receive either

evacetrapib 130 mg daily or placebo daily. Patients will receive, at the discretion of their treating physician, standard therapy for HRVD (for example, aspirin, antihypertensives, and antiplatelets, as dictated by local guidelines and standard of care). Standard therapy is expected to include appropriate diet and exercise and other nonpharmacologic measures. Patients will receive evidence-based management of LDL-C (and TG) to appropriate guideline-driven target levels throughout the study, and are to be on statin therapy throughout the study unless statin intolerant or contraindicated for statins.
The study will continue until at least 1400 patients reach the primary composite endpoint; with at least 700 patients experiencing 1 or more of the composite endpoint of cardiovascular (CV) death, myocardial infarction (MI), or stroke; and at least 1.5 years after the last patient entered treatment. The anticipated median duration of treatment is approximately 3 years, with >80% of patients expected to complete at least 2.5 years of follow-up. The anticipated maximum duration of treatment is expected to be up to 4 years.
All endpoints will be independently adjudicated by a Clinical Endpoints Committee (CEC). An independent Data Monitoring Committee (DMC) will review unblinded data to ensure patient safety during the conduct of the study.

Intervention

Eligible patients in stable condition (as judged by the responsible physician) and who meet all entry criteria will be randomized to receive either evacetrapib 130 mg daily or placebo daily.

Study burden and risks

Data from previous studies with Evacetrapib showed that Evacetrapib can be used safely in humans. Treatment with Evacetrapib resulted in a decrease of LDL cholesterol and an increase in HDL cholesterol. This results justify this phase III study in which efficacy of Evacetrapib and the consequences of these cholesterol changes are examined further.

The standard care for this group of patients consist of medication and in most cases also lifestyle advices like a diet and exercise instructions. The patient is known with use of medication and frequent visits to the hospital. The amount of visits that should be done for this trial is more often compared to regular care. This can be experienced as a burden for the subject. Also the amount of tests and procedures during the visits will be more compared to standard care. Skin rash is most important side effect that is seen in previous studies with Evacetrapib. This skin rash was resolved after treatment. Side-effects that are seen in medication that is comparable to Evacetrapib where not seen in the studies with Evacetrapib. Possible risks related to the study procedures are; risk of skin irritation of the ECG pads and risk of hematoma's, dizziness, discomfort and pain at blood draw. These risks (of Evacetrapib and study procedures) can be described as mild.

The subject will be informed about this potential risks and burden extensively before consent is obtained (both written and oral). By means of that, the subject can determine what is acceptable for him/ her and make a well thought decision.

Risks and issues related to patient safety are avoided as much as possible by means of the study design. For example in- and exclusion criteria, safety assessments and follow up. The study team will monitor patient safety carefully. Besides that there is data safety monitoring board involved.

Contacts

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Eli Lilly and Company

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients with HRVD are defined by at least 1 of the following 4 groups. Note that an eligible

patient may meet inclusion criteria for more than 1 group.;1) History of ACS (that is, *30 days through 365 days after discharge for ACS)
For the purposes of this study, ACS will include 1) unstable angina and non-ST-segment elevation myocardial infarction [UA/NSTEMI] and 2) ST-segment elevation myocardial infarction [STEMI] as follows:
* UA is defined as a history of chest discomfort or ischemic symptoms of *10 minutes duration at rest with persistent or transient ST-segment deviation *1 mm in 1 or more electrocardiogram (ECG) leads without elevation of creatine kinase-myocardial bands (CK-MB) or troponin T or I.
* NSTEMI is defined as a history of chest discomfort or ischemic symptoms of *10 minutes duration at rest with no evidence of persistent ST-segment elevation. Patients must also have CK-MB or troponin T or I greater than the 99th percentile upper reference limit or the upper limit of normal (ULN). If CK-MB or troponin is not available, total CK greater than 99th percentile upper reference limit (or ULN) is acceptable.
* STEMI is defined as a history of chest discomfort or ischemic symptoms of >20 minutes duration at rest with 1 of the following present on at least 1 electrocardiogram (ECG) prior to randomization:
a. ST-segment elevation *1 mm in 2 or more contiguous ECG leads
b. New or presumably new left bundle branch block (LBBB)
c. ST-segment depression *1 mm in 2 anterior precordial leads with clinical history and evidence suggestive of true posterior infarction;Patients will have either undergone successful coronary revascularization associated with the ACS event prior to date of anticipated randomization or are not anticipated to undergo coronary revascularization.
Patients will NOT qualify for the trial on the basis of MI related to revascularization intervention (either percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery) performed outside the setting of an acute ACS.;2) Cerebrovascular Atherosclerotic Disease
* History of transient ischemic attack (TIA) or ischemic stroke (*30 days) with carotid stenosis *50% in the distribution of the clinical event, or
* Asymptomatic carotid artery stenosis *70%, or
* A history of carotid artery revascularization;3) Peripheral Arterial Disease
Peripheral arterial disease (PAD) for this study will be defined as current intermittent claudication or resting limb ischemia and either an ankle-brachial index (ABI) *0.90, or a history of atherosclerotic limb ischemia leading to previous noncoronary revascularization or amputation.
Patients will NOT qualify for the trial on the basis of isolated renal artery stenosis in the absence of other inclusion criteria.;4) Diabetes Mellitus with Documented Coronary Artery Disease
Diabetes mellitus (DM) patients are defined as either receiving concomitant treatment with an oral or parenteral hypoglycemic agent and/or insulin, or being managed by diet alone, as a result of a preexisting diagnosis of DM. A new diagnosis is based on plasma glucose measurements or glycated hemoglobin (HbA1c) levels (with anticipated treatment with an oral or parenteral hypoglycemic agent and/or insulin, or to be managed by diet alone).
Patients with DM must have CAD documented by a previous MI, PCI, CABG, or >50% angiographic stenosis of *1 major coronary artery.;Patients are eligible to be included in the study only if they meet all of the following criteria:
[1] Males or females *18 years of age with a diagnosis of HRVD (that is, meet at least 1 of the

disease diagnostic criteria described above), and are clinically stable (as judged by the responsible physician)
[2] Must be treated with a statin for at least 30 days prior to screening. If not treated with a statin, patients must have documented statin intolerance, or contraindication to statin (as defined in the protocol)
[3] Have a screening HDL-C *80 mg/dL (*2.1 mmol/L)
[4] Have screening triglycerides (TG) *400 mg/dL (*4.5 mmol/L)
[5] Meet 1 of the following criteria:
a) screening LDL-C no more than 10 mg/dL (0.3 mmol/L) above the target chosen by the investigator (either LDL-C <100 mg/dL [<2.6 mmol/L] or LDL-C <70 mg/dL [<1.8 mmol/L])
OR
b) if LDL-C is greater than target, the patient must be on maximum tolerated statin dose (for at least 30 days), have documented statin intolerance, or contraindication to statin
[6] At the time of screening, are able and willing to give written informed consent

Exclusion criteria

Patients will be excluded from the study if they meet any of the following criteria:;General Exclusion Criteria:;[7] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted;[8] Are Lilly employees or are employees of the Academic Research Organization (ARO) or Clinical Research Organization (CRO) (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly employees may participate in Lilly-sponsored clinical studies but are not permitted to participate at a Lilly facility. Immediate family is defined above;[9] Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational product or nonapproved use of a drug or device (other than the investigational product used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study;[10] Have previously completed or withdrawn from this study, or withdrawn from any other study investigating evacetrapib;Medical Conditions Exclusion Criteria:;[11] Females who are known to be pregnant;[12] Females who are breastfeeding;[13] Women of child-bearing potential only (that is, women who are not surgically or chemically sterilized and who are between menarche and 1 year postmenopause), who test positive for pregnancy between screening and randomization (based on the required urine or serum pregnancy test) or who do not agree to use a reliable method of birth control during the study;[14] History of transient ischemic attack (TIA) or ischemic stroke <30 days and ACS <30 days;[15] Any reading of systolic blood pressure *180 mm Hg or diastolic blood pressure *110 mm Hg at screening or randomization;[16] History of hemorrhagic stroke or intracranial hemorrhage;[17] New York Heart Association class III or IV congestive heart failure;[18] Serum creatinine >2.2 mg/dL (>194.5 *mol/L) at screening;[19] Clinically active liver disease (for example, esophageal varices, jaundice, ascites, cholestasis, acute or chronic hepatitis). Patients are not excluded due to Gilbert*s Syndrome or a history of cholelythiasis/cholecystectomy;[20] History of malignancy (except for nonmelanoma skin cancer/basal cell or squamous cell carcinoma of the skin) within the preceding 3 years prior to screening;[21] Known malabsorption syndrome

with the exception of lactose intolerance;[22] Patients with a known history of primary or secondary hyperaldosteronism;[23] Patients with a history of intolerance/hypersensitivity to cholesterol ester transfer protein (CETP) inhibitors;[24] Any clinically significant medical condition that according to the investigator could interfere with participation in the study;[25] Patients whose life expectancy is anticipated to be less than 4 years;[26] Unable or unwilling to comply with protocol requirements, or deemed by the investigator to be unfit for the study;[27] Have a history of drug, alcohol, or substance abuse within the past 6 months, as assessed by the investigator;Prior/Concomitant Therapy Exclusion Criteria:;[28] Concurrent or anticipated need for treatment with niacin >250 mg/day ;[29] Concurrent or anticipated need for chronic administration of drugs on the exclusion list;[30] Previous exposure to (or participation in a trial of) the CETP inhibitors dalcetrapib or evacetrapib within the last 3 months or anacetrapib within the last 12 months.;Procedure Exclusion Criteria:;[31] Any planned coronary angiography or coronary revascularization procedure. If angiography or revascularization is planned, patients may be screened and enrolled after all such planned procedures are completed

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):	07-05-2013
Enrollment:	679
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Evacetrapib
Generic name:	Evacetrapib

Ethics review

Approved WMO Date:	13-03-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	03-04-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-06-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	29-07-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-04-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	01-05-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	07-05-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-05-2014
Application type:	Amendment

Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-12-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-09-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-01-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-06-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-07-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2012-000061-21-NL
CCMO	NL42284.058.12