A Phase 2 Efficacy and Safety Study of LY2484595 Alone and in Combination with Atorvastatin, Simvastatin, and Rosuvastatin in Patients with Hypercholesterolemia or Low HDL-C.

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The primary objective of this study is to determine whether LY2484595, administered incombination with atorvastatin for 12 weeks to patients with hypercholesterolemia or low HDL-C, will significantly increase mean HDL-C and decrease mean LDL-C from...

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

Summary

ID

NL-OMON36417

Source
ToetsingOnline

Brief title
EIAF

Condition

- Lipid metabolism disorders

Synonym
Low HDL-C and Hypercholesterolemia

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Industrie: Eli Lilly and Company;Indianapolis;Indiana USA

Intervention

Keyword: CETP, dyslipidemia

Outcome measures

Primary outcome

Efficacy:

High-density lipoprotein cholesterol and direct LDL-C will be measured. After

Visit 1, a central laboratory will be used for these measurements.

Safety:

Treatment-emergent adverse events (TEAEs), SAEs, assessment and management of

patients developing rash, vital signs and physical examinations including

systolic and diastolic blood pressure and pulse rate, centrally adjudicated

cardiovascular events, ECGs, glucocorticoid activity, mineralocorticoid

activity, muscle injury, liver injury, and additional laboratory measurements.

Secondary outcome

Efficacy:

The following secondary efficacy measures will be collected. All measurements

after Visit 1 will be determined by a central laboratory.

* Total cholesterol, non-HDL-C, VLDL cholesterol, TG

* Inflammatory biomarkers (hsCRP, MPO)

* Lipid nuclear magnetic resonance (NMR) (lipoprotein particle size and number

by NMR)

* Apolipoprotein panel (Apo A-I, Apo A-II, Apo C-II, Apo C-III, Apo E, Apo

B-total)

Health Outcomes:

EQ-5D.

Bioanalytical:

Plasma samples will be assayed for LY2484595, statin parent, and statin

metabolites using a validated LC/MS/MS method.

Pharmacokinetic/Pharmacodynamic:

Venous blood samples will be obtained to measure the plasma concentrations of

LY2484595 and the following statin parent and statin metabolites: atorvastatin,

o-hydroxyatorvastatin, p-hydroxyatorvastatin, rosuvastatin, rosuvastatin

lactone, N-desmethyl rosuvastatin, simvastatin, and simvastatin acid. Venous

blood samples will also be collected to measure CETP activity and mass.

Study description

Background summary

Atherosclerosis remains a major health burden on developed societies and is an emergingproblem in underdeveloped countries. Aggressive lowering of low-density lipoproteincholesterol (LDL-C) has demonstrated 20-35% relative reductions in cardiovascular events. However, there remains a need for additional therapies targeting other lipidrelated risk factors to address the residual cardiovascular disease (CVD).

High-density lipoprotein cholesterol (HDL-C) is an emerging target for lipid modification. Based on substantial epidemiological evidence, HDL-C levels are inversely correlated with CVD risk. Potential anti-atherogenic properties of HDL include promotion of reverse cholesterol transport, antiapoptotic effects, inhibition of platelet activation and coagulation cascade, anti-inflammatory and anti-oxidant effects, and enhancement of endothelial function. One mechanism for increasing HDL-C concentration is inhibition of the plasma glycoprotein cholesteryl ester transfer protein (CETP). CETP mediates the transfer of cholesteryl ester (CE) from HDL to apo B-rich lipoproteins, including LDL and verylow-density lipoprotein (VLDL), in exchange for their triglycerides (TG).Inhibition of CETP activity with torcetrapib reduced the progression of atherosclerosis in rabbits (Morehouse et al. 2007); however, the hypothesis that increasing HDL-C by inhibiting CETP reduces the risk of CVD has yet to be confirmed in a clinical outcome trial. Torcetrapib was the first oral CETP inhibitor to reach an advanced stage of clinical development. The clinical outcome trial, ILLUMINATE, was prematurely stopped due to an excessive rate of mortality (Barter et al. 2007; Rader 2007). This comprised a numerically greater incidence of death due to both cardiovascular and non-cardiovascular causes. Three clinical imaging trials also demonstrated that administration of torcetrapib did not slow progression of atherosclerosis within the coronary and carotid arteries (Bots
et al. 2007; Kastelein et al. 2007; Nissen et al. 2007). Subsequent analysis revealed evidence of slowing of disease progression with increasing levels of HDL-C, suggesting that an off-target toxicity was more likely to have contributed to the toxicity of torcetrapib, rather than a mechanism-related effect (Nicholls et al. 2008). The experience that torcetrapib elevated blood pressure, in combination with the finding that
it promotes adrenal release of aldosterone and cortisol (Hu et al. 2009), point to potentialmolecule-specific toxicities of torcetrapib.

Study objective

The primary objective of this study is to determine whether LY2484595, administered incombination with atorvastatin for 12 weeks to patients with hypercholesterolemia or low HDL-C, will significantly increase mean HDL-C and decrease mean LDL-C from baseline to endpoint, compared to atorvastatin alone.

The secondary objectives of the study are as follows:
* To demonstrate whether LY2484595 administered as monotherapy significantly increases mean HDL-C and decreases mean LDL-C compared to placebo.
* To evaluate the additive PD effects of LY2484595 administered in combination with simvastatin or rosuvastatin on mean HDL-C and LDLC.
* To evaluate the PK of LY2484595 in the presence of atorvastatin, simvastatin, and rosuvastatin.
* To evaluate the effect of LY2484595 on plasma CETP activity and mass in the presence of statins.
* To evaluate the effect of LY2484595 on the PK/PD profile of atorvastatin,

simvastatin, and rosuvastatin.
* To evaluate the dose-response, exposure-response, and time-response relationships for HDL-C and LDL-C over a 12-week time course for LY2484595 as monotherapy and in combination with atorvastatin, simvastatin, and rosuvastatin.
* To assess for interactions between baseline characteristics (e.g., HDL-C, LDL-C, TG) and lipid response to therapy.
* To evaluate the effects of LY2484595 as monotherapy and in combination with statins on safety and tolerability.
* To evaluate the incidence and severity of rashes with LY2484595 and potential relationship to study drug.
* To evaluate the effect of LY2484595 on blood pressure, aldosterone, plasma renin activity, plasma potassium, serum sodium, and serum bicarbonate compared with placebo, and to assess for a correlation between LY2484595 exposure and blood pressure or measures of mineralocorticoid activity.
* To assess whether LY2484595 has an effect on the incidence of statinrelated safety concerns, including myopathy and liver injury.
* To evaluate the effects of LY2484595 on exploratory biomarkers associated with the risk of atherosclerosis (e.g., hsCRP, MPO).
* To examine test-retest stability of patient-reported outcomes instrument EuroQol-5 dimensions (EQ-5D) and mean change in baseline utility score at end of study. The Visual Analog Scale (VAS) and overall utility score will be the primary variables of interest.

Study design

Study EIAF is an outpatient, multicenter, randomized, double-blind, double-dummy, parallel group, placebo- and active-controlled, Phase 2, efficacy and safety study in approximately 400 patients with hypercholesterolemia or low HDL-C. Patients will be stratified according to baseline levels of serum TG (<150 or *150 mg/dL), HDL-C (<45 or *45 mg/dL for men; <50 or *50 mg/dL for women), and region (United States or Europe).

The study will compare LY2484595 as monotherapy to placebo, and LY2484595 in combination with each of the 3 statins (atorvastatin, simvastatin, and rosuvastatin) to each respective statin alone. Three doses (30 mg, 100 mg, 500 mg) of LY2484595 will be evaluated as monotherapy. A single dose of LY2484595 (100 mg) will be evaluated in combination with each of the 3 statins.

The study design includes 4 consecutive phases: a Screening Phase, a Diet Lead-In/Washout Phase, an Active Treatment Phase, and a Follow-up Phase. Patient participation may range between 19 and 41 weeks.

Intervention

This study involves a comparison of LY2484595 (30, 100 and 500 mg once daily) as monotherapy, LY2484595 100 mg in combination with each of the statins: atorvastatin 20 mg, simvastatin 40 mg, and rosuvastatin 10 mg, each statin alone and placebo. Table EIAF.2 shows the treatment regimens.
There will be 10 treatment groups in total.

The monotherapy treatment and placebo groups are as follows:
-LY2484595 (30 mg once daily) Group 1
-LY2484595 (100 mg once daily) * Group 2
-LY2484595 (500 mg once daily) * Group 3
-Placebo * Group 4

The combination therapy treatment and active comparator groups are as follows:
-LY2484595 (100 mg once daily) + atorvastatin 20 mg once daily * Group 6
-LY2484595 (100 mg once daily) + simvastatin 40 mg once daily * Group 8
LY2484595 (100 mg once daily) + rosuvastatin 10 mg once daily * Group 10
-atorvastatin 20 mg once daily * Group 5
-simvastatin 40 mg once daily * Group 7
-rosuvastatin 10 mg once daily * Group 9

Study burden and risks

The study design includes 4 consecutive phases: a screening phase of up to 5 weeks duration; a diet lead-in/washout phase of up to 18 weeks duration (based on preexisting lipid-modifying medication, which has to be stopped after Visit 1); an active treatment phase of 12 weeks duration (to allow for prediction of the maximal lipid effects of LY2484595); and a follow-up phase of up to 6 weeks duration. A placebo-only arm will be included to allow LY2484595 monotherapy comparisons. The study allows only inclusion of patients with hypercholesterolemia or
low HDL-C without clinical manifestations of CHD. Patient participation may range between 19 and 41 weeks, depending on the duration of time required to wash out the effects of the different lipid-related concomitant medications. Therefore, some patients could possibly not receive any lipid-modifying therapy for a maximum of 41 weeks. In order to minimize the risk of allowing LDL-C values to go untreated during the duration of the study, the inclusion criteria require that patients have LDL-C levels that fall within an acceptable range according to the patient*s risk of CHD based on National Cholesterol Education Program Adult Treatment Panel III guidelines. Furthermore, patients who qualify for entry into Study EIAF will be instructed to follow a low-fat diet in accordance with regional guidelines (for example, the American Heart Association or EuropeanSociety of Cardiology) for the duration of the study.

Safety Considerations and Potential Risks Associated with LY2484595. The

treatment-emergent adverse events (TEAEs) that occurred with LY2484595 treatment in Studies EIAA and EIAB and were considered possibly related to LY2484595 by the investigator (TEAEs reported by 2 or more subjects) included diarrhea, dizziness, headache, fatigue, rash, pruritis, decreased appetite, flatulence, and palpitations. No events were considered related to study drug in Study EIAG or EIAD to date. In the 3 clinical studies of LY2484595, there were no clinically relevant changes from baseline in laboratory values, vital signs or corrected QT interval (QTc) after administration of single or multiple doses of LY2484595. The potential risks associated with LY2484595, and the approaches for monitoring and mitigating these risks to patients enrolled in Study EIAF, are as follows:

Rash.
Four maculopapular rashes were observed among 63 healthy subjects who were treated with LY2484595 in Study EIAB: 2 with the 300-mg dose and 2 with 600 mg. All were considered to be related to study drug by the investigator and were mild or moderate in severity. One serious adverse event occurred after a subject received 8 doses of LY2484595 and was hospitalized for evaluation and treatment of fever and rash.
Study EIAF will further investigate the occurrence of rash in patients with dyslipidemia treated with LY2484595. Patients at risk for developing a drug-related rash will be excluded as detailed in the protocol. Investigators will be trained to monitor patients for rash, and if rash occurs, to evaluate the rash as detailed in the study protocol.

Blood Pressure Increase and Changes in Mineralocorticoid Activity.
Blood pressure increase and changes in mineralocorticoid activity were observed in Phase 3 studies of torcetrapib (Barter et al. 2007; Rader 2007). Although Phase 1 data with LY2484595 do not suggest any clinically significant effects on blood pressure or mineralocorticoid activity in healthy subjects, Study EIAF will further investigate the effects of LY2484595 on blood pressure, mineralocorticoid activity (that is, aldosterone, plasma renin activity, serum sodium and bicarbonate, and plasma potassium), and salivary cortisol in patients with dyslipidemia. Patients with poorly controlled blood pressure or electrolyte disorders are excluded from participation. To maximize the probability of detecting a blood
pressure increase, investigators will monitor vital signs for clinically significant changes. Repeat standardized measurements using automated blood pressure devices will enable detection of potential clinically relevant blood pressure signals. Furthermore, because the
blood pressure increase observed in Phase 2 studies of torcetrapib was not clearly evident after 8 weeks of dosing (Davidson et al. 2006; McKenney et al. 2006), a longer 12-week treatment period may increase the ability to detect a potential blood pressure signal.

Drug-Drug Interactions (DDI).
LY2484595 is likely a weak CYP3A inhibitor. Statins are known CYP3A substrates,

and higher exposures to statins are associated with adverse effects on skeletal muscle and liver. In addition, in vitro testing suggests that LY2484595 is an inhibitor of the organic anion transporter protein 1B1 (OATP1B1); thus, it may decrease the lipid-lowering effect of statins. Study EIAF will assess the potential for DDIs between LY2484595 and the 3 statins, and in particular investigate whether LY2484595 has an effect on the incidence of statin-related safety concerns, including myopathy or liver injury. No adverse effect of LY2484595 on liver or muscle is expected based on Phase 1 data and nonclinical toxicology studies. To minimize the risk of DDI in Study EIAF, the use of inducers or moderate or strong inhibitors of CYP3A, potent inhibitors of the OAT1B1 drug transporter, and patients with elevated liver enzymes or creatine kinase (CK) or a history of statin intolerance will be excluded. Investigators will be trained to monitor patients for signs and symptoms of statin-related safety concerns and to review laboratory reports for elevations in liver enzymes and CK and, if identified, to manage such findings as detailed in the protocol.

Liver Enzyme Increase.
Two out of 63 healthy subjects who received multiple daily doses of LY2484595 in Study EIAB experienced >2-fold increases in aspartate aminotransferase, without accompanying increases in alanine aminotransferase or total bilirubin outside of the normal range. Nonclinical data do not suggest a potential hepatotoxic effect of LY2484595. Patients with (or with the potential for) elevations in liver enzymes will be excluded from Study EIAF. Investigators will monitor liver enzymes in Study EIAF and manage elevations as detailed in the protocol.

QT Interval Prolongation.
Although no clinically remarkable changes in QTc were observed in healthy subjects in completed Phase 1 studies of LY2484595, nonclinical studies suggest that LY2484595 may have a potential QTc prolongation effect. Patients at risk for QTc prolongation will be excluded from Study EIAF. Electrocardiograms will be performed at each visit. If a clinically significant increase in the QTc interval is detected, the investigator should manage the patient as detailed in the protocol.

Fetal Abnormalities.
Decreased fetal weight and fetal malformations were observed at a high dose of LY2484595 that produced severe maternal toxicity in pregnant rats. To minimize this risk in Study EIAF, appropriate precautions will be taken to exclude pregnant women, and women of child-bearing potential must agree to use a reliable method of birth control during the study and for 2 weeks following the last dose of study drug. Any pregnancy that does occur will be monitored appropriately and the woman will be discontinued from treatment.

Increased Incidence of Fatal Events.
The Phase 3 study with torcetrapib was prematurely stopped due to an excessive

rate of mortality comprised of a numerically greater incidence of death due to both cardiovascular and non-cardiovascular causes (Barter et al. 2007; Rader 2007). Because of this cardiovascular risk associated with the first compound of this pharmaceutical class, major cardiovascular events that may occur in Study EIAF will be assessed using a blinded central adjudication committee. Since patients with clinical manifestations of CHD will be excluded from participating, major
cardiovascular events are expected to be rare in this 12-week study.

Contacts

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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

Male or female patients with hypercholesterolemia or low HDL-C who are 18 years of age or older and have given informed consent are eligible to participate in this study.;Other criteria

for inclusion include:
* Diagnosed with low HDL-C or hypercholesterolemia, after diet lead-in/washout of lipid therapies.;Low HDL lipid criteria:
- HDL-C <45 mg/dL (1.16 mmol/L) (men) and <50 mg/dL (1.29 mmol/L) (women), and
- LDL-C according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines , as follows:
- LDL-C <190 mg/dL (4.91 mmol/L) (0-1 risk factors)
- LDL-C <160 mg/dL (4.14 mmol/L) (2+ risk factors: 10-year CHD risk of <10%)
- LDL-C <130 mg/dL (3.36 mmol/L) (2+ risk factors: 10-year CHD risk of 10-20%)
- LDL-C <100 mg/dL (2.59 mmol/L) (diabetics), and
- Fasting TG <400 mg/dL (4.52 mmol/L)
OR
High LDL-C lipid criteria:
- LDL-C according to NCEP ATP III guidelines;factors and determination of 10-year CHD risk), as follows:
- LDL-C 100-190 mg/dL (2.59 mmol/L-4.91 mmol/L) (0-1 risk factors)
- LDL-C 100-160 mg/dL (2.59 mmol/L-4.14 mmol/L) (2+ risk factors: 10-year CHD risk of <10%)
- LDL-C 100-130 mg/dL (2.59 mmol/L-3.36 mmol/L) (2+ risk factors: 10-year CHD risk of 10-20%)
- Any HDL-C, and
- Fasting TG <400 mg/dL (4.52 mmol/L);Note: The MOO provides guidance regarding on-treatment lipid levels that would
support entering Diet Lead-in/Washout Phase. Patients with diabetes may be eligible
only based on low HDL-C criteria.
* Male patients who agree to use a reliable method of birth control during the study (and for 2 weeks following the last dose of study drug).
* 1) Women not of childbearing potential due to surgical sterilization (hysterectomy, bilateral oopherectomy, or tubal ligation) or menopause. Postmenopausal is defined as women age *45 with an intact uterus who have not taken hormones or oral contraceptives within the last year and who have had either cessation of menses for at least 1 year, or 6 to 12 months of spontaneous amenorrhea with follicle-stimulating hormone (FSH) >40 mIU/mL (40 IU/L) OR 2) Women of child bearing potential who have a negative urine or serum pregnancy test and agree to use a reliable method of birth control (for example, injectable or implantable contraceptives [for example,
Norplant®]; contraceptive transdermal patch; a reliable barrier method of birth control; or intrauterine device) during the study and for 2 weeks following the last dose of study drug.

Exclusion criteria

Main criteria for exclusion include:
* Have recent history (within 1 month of screening) of any clinically significant rash, history of any clinically severe drug-related rash, history of a chronic skin disorder (such as psoriasis, eczema, or urticaria), history of significant skin hypersensitivities to household or cosmetic products, or allergens per the investigator, or presence of widespread tattoos or other skin

condition that limits the assessment for rashes. Patients who develop any rash during the Diet Lead-in/Washout Phase cannot be randomized.
* Have or have had any clinical manifestation of coronary heart disease (CHD), such as stable or unstable angina, acute coronary syndrome, myocardial infarction, or a coronary revascularization procedure, including stent placement, symptomatic carotid artery disease, peripheral arterial disease, or abdominal aortic aneurysm.
* Have systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg as determined by the mean of 3 standardized measurements in the sitting position at Visit 3
* Have documented hyperaldosteronism.
* Have symptoms consistent with moderate or severe heart failure or are receiving treatment for symptomatic congestive heart failure (CHF) or known left ventricular ejection fraction (LVEF) <35%. The absence of LVEF measurement does not prohibit entry into this study.
* Have one of the following abnormalities: QTc prolongation (Bazett*s corrected QTc interval [QTcB]) of >450 msec in male patients or >470 msec in female patients, or abnormally wide QRS complexes (resulting from bundle branch blocks, intraventricular conduction delays, or pacemakers) or atrial fibrillation on screening electrocardiogram (ECG), previous history of QTc prolongation with another medication that required discontinuation, congenital long QT syndrome, previous history of ventricular tachycardia or unexplained syncope.
* Have active hepatobiliary disease, serologic evidence of past or active hepatitis B or C, or past or active gallbladder disease. Patients who have been diagnosed with Gilbert syndrome or had a cholecytectomy greater than 3 months prior to enrollment can be included.
* Have aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), or total bilirubin >1.5 times the upper limit of normal (ULN).
* Have a history or presence of a chronic muscular or neuromuscular disease including prior rhabdomyolysis or drug-induced myopathy or an unexplained/documented elevation in creatine kinase (CK) >3 times ULN.
* Have a history of discontinuation from statin, change of statin, or a dose reduction of statin due to history of hypersensitivity, intolerance, or adverse effect. Have a history of increased hepatic enzymes associated with use of an HMG-CoA reductase inhibitor (statin).
* Have hemoglobin A1c *8.0%; or use, plan to use, or are likely to require insulin during the course of the study. Diabetic patients on an antidiabetic agent with lipid modifying effects must be on a stable dose for at least 1 month prior to screening to be eligible for the study.
* Have a serum creatinine *2 mg/dL (153 *mol/L), or nephrotic syndrome, end-stage renal disease and use renal replacement therapy such as hemodialysis or peritoneal dialysis.
* Have hemoglobin <10 gm/dL (6.2 mmol/L) in women and <11 gm/dL (6.83 mmol/L) in men.
* Have current uncontrolled active inflammatory condition or infection which in the opinion of the investigator would influence a patient*s ability to complete the study.
* Have thyroid-stimulating hormone (TSH) levels outside normal reference range. Patients who are clinically euthyroid, on stable thyroid replacement therapy for 2 months prior to screening, and are anticipated to remain on this dose throughout the trial period are acceptable exceptions to this criteria.
* Have planned or are likely to require major surgery requiring anesthesia or hospitalization during the course of the study.
* Have chronic alcohol or drug abuse or dependency.
* Are currently under suspicion of having cancer or have had a history of cancer in the past 2 years, with the exception of excised superficial lesions such as basal cell carcinoma and squamous cell carcinoma of the skin.

* Plan to use, are likely to require, or unwilling or unable to stop with adequate washout any prescription or over-the-counter (OTC) medication or health foods with the intent to treat serum lipids (LDL-C, HDL-C, TG) including but not limited to these classes of drugs: statin, fibrate, ezetimibe, niacin, bile acid sequestrant, fish oil.
* Patients taking niacin >1000 mg/day are excluded from the study.
* Patients taking niacin 251 to 1000 mg/day or fibrates are excluded from study entry on or after 01 September 2010.
* Are currently using, plan to use, or are likely to require during the course of the study systemic corticosteroids; or anabolic agents other than stable doses of estrogen, estrogen/progestin, or testosterone replacement therapy.
* Are currently using, plan to use, or are likely to require during the course of the study, more than the occasional use (that is, once per month) of stimulant laxatives (for example, bisacodyl), osmotic laxatives (for example, milk of magnesia), or castor oil.
* Use of any immunosuppressive therapy within 2 months prior to screening or are likely to require immunosuppressive therapy during the course of the study.
* Have received treatment within 30 days prior to the time of study entry with any drug or drugs that have not received regulatory approval for any indication.
* Have participated within 3 months prior to screening visit in any clinical trials of CETP inhibitors (for example, anacetrapib or dalcetrapib).
* Are currently adhering to, have used within 2 months prior to screening, or have plans to adopt diets with aggressive carbohydrate restrictions for weight loss, including but not limited to Atkins® or South Beach® diets. Or currently use, have used within 2 months prior to screening, or plan to use during the trial period prescriptions or over-the-counter (OTC) formulations intended for weight loss.
* Are currently using, have used within 2 months prior to screening visit, plan to use, or are likely to require during the course of the study, drugs or foods that are inducers (including rifampin and carbamazepine) of moderate or strong inhibitors of cytochrome P450 3A (including, ketoconazole, erythromycin, and grapefruit juice); or strong inhibitors of the OATP1B1 transporter (including cyclosporine and rifampin).

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2010
Enrollment:	60
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Crestor
Generic name:	rosuvastatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lipitor
Generic name:	atorvastatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Zocor
Generic name:	Simvastatin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	23-04-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-07-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-10-2010
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-02-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2009-017479-29-NL
CCMO	NL31256.018.10