A placebo-controlled, double-blind, randomized trial to compare the effect of treatment on plaque burden as determined by intravascular ultrasound and to evaluate the efficacy, pharmacokinetics, safety, and tolerability of MDCO-216 given as multiple weekly infusions in subjects with a recent acute coronary syndrome.

Published: 17-11-2015
Last updated: 19-03-2025

Primary ObjectivesTo evaluate the effect of MDCO-216 treatment on the change in PAV of a target coronary artery as measured by IVUS imaging following five weekly infusions of MDCO-216 (20 mg/kg) compared with placebo in subjects with a recent ACS....

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

Summary

ID

NL-OMON43722

Source
ToetsingOnline

Brief title
MILANO PILOT

Condition

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

Synonym
Atherosclerosis and plaque burden

Research involving
Human

Sponsors and support

Primary sponsor: Medicines Company
Source(s) of monetary or material Support: The Medicines Company

Intervention

Keyword: acute coronary syndrome, Atherosclerosis, Plaque burden, Proof of concept

Outcome measures

Primary outcome

The primary outcome of this trial is the change in PAV from baseline to Day 36

post randomization, as determined by IVUS.

The primary variable of change in PAV will be computed as follows: PAV (Week 6)

* PAV (baseline)

Secondary outcome

The secondary outcome trial are:

-Change in TAV from baseline to Day 36 post-randomization, as determined by IVUS

-Change in TAV for the 10 mm subsegment with the greatest disease burden at

baseline

-The proportion of subjects in each group with regression of coronary

atherosclerosis, defined as a reduction in PAV from baseline to Day 36 of more

than 2 standard deviations of the test-retest variability.

-Proportion of subjects in each group with regression of coronary

atherosclerosis, defined as a change in PAV from baseline to Day 36 of less

than zero.

Study description

Background summary

MDCO-216 is being developed as a disease-modifying treatment for subjects with atherosclerotic disease including CAD to limit disease progression by reducing the cholesterol deposition in arterial walls and reduce the occurrence of atherothrombotic events.

MDCO-216 is a complex of recombinant ApoA-IM (rApoA-IM) and POPC. This complex is designed to mimic HDL in structure and function, to promote RCT. This complex is assumed to mimic the nascent HDL particle in both structure and function. MDCO-216 is anticipated to have therapeutic utility as an agent to acutely regress atherosclerotic plaque burden, particularly so-called vulnerable plaques, by reducing the size of the lipid core, and therewith improve outcomes in patients with atherosclerotic disease including ACS patients.

This protocol describes a study to compare the effect of treatment with MDCO-216 on plaque burden as measured by intravascular ultrasound (IVUS) and to evaluate the efficacy, pharmacokinetics (PK), safety, and tolerability of multiple doses of MDCO-216 in subjects with a recent ACS who will be treated with MDCO-216 within 14 days of presentation with the ACS.
MDCO-216 is an investigational disease-modifying treatment under development by The Medicines Company (MDCO) for the regression of atherosclerotic plaque burden and reduction of clinical events in acute coronary syndrome (ACS) patients

Study objective

Primary Objectives
To evaluate the effect of MDCO-216 treatment on the change in PAV of a target coronary artery as measured by IVUS imaging following five weekly infusions of MDCO-216 (20 mg/kg) compared with placebo in subjects with a recent ACS.

Secondary Objectives
To evaluate the effect of MDCO-216 on the following additional atheroma parameters measured by IVUS:

- Change in TAV.
- Change in TAV in the 10 mm subsegment containing the most amount of disease at baseline.
- Proportion of subjects who demonstrate regression of coronary atherosclerosis, defined as a change PAV of less than zero (ie, any reduction in PAV) or 2 standard deviations of the test/re-test variability.

Safety Objectives
- To evaluate the safety profile of MDCO-216.

Study design

This study will be a Phase IIa placebo-controlled, double-blind, randomized trial in subjects with a recent ACS, to evaluate the efficacy, PK, safety, tolerability, disease progression measures by IVUS, and PD of MDCO-216 infusion. Approximately 120 subjects will be enrolled at approximately 20-30 centers. Informed consent will be obtained from subjects before the initiation of any study-specific procedures. Eligible subjects will be randomized to receive 5 infusions of MDCO-216 20 mg/kg or placebo in a 1:1 ratio. The infusions will be given once weekly over a 5-week period.
The endpoints of this trial are to investigate the efficacy, safety, tolerability, PK, and PD of MDCO-216 in subjects with a recent ACS. The evaluation of these endpoints will be based on an assessment of IVUS imaging parameters, safety and tolerability (AEs, ECG, vital signs, infusion reactions, laboratory parameters, PD: as measured by effects of MDCO-216 on plasma lipid profiles such as ex-vivo cholesterol efflux capacity, as a reflection of the first step of reverse cholesterol transport, and other relevant pharmacodynamic parameters). Subjects will be identified for eligibility on the basis of a recent ACS requiring coronary angiography for further clinical evaluation.

The first 24 subjects who are enrolled and randomized to MDCO-216 or placebo at selected sites with the capabilities to meet the detailed PK requirements, will undergo blood sampling for extensive PK analysis. PK analysis will not be performed in those subjects who receive placebo.
The purpose of this PK substudy is to evaluate PK parameters after Infusion 1 and Infusion 5 of MDCO-216.

Intervention

This study will be a Phase IIa, placebo-controlled, double-blind, randomized trial in 120 subjects with a recent ACS, to evaluate the efficacy, PK, safety, tolerability, disease progression measures by IVUS, and pharmacodynamics (PD) of MDCO-216 infusion.
Subjects will be randomized to receive placebo or MDCO-216 20 mg/kg in a 1:1 treatment allocation ratio stratified by country and previous statin use. Each subject will receive five IV infusions of blinded study drug.

The first 24 subjects who are enrolled and randomized to MDCO-216 or placebo at selected sites with the capabilities to meet the detailed PK requirements, will undergo blood sampling for extensive PK analysis. PK analysis will not be performed in those subjects who receive placebo.
The purpose of this PK substudy is to evaluate PK parameters after Infusion 1 and Infusion 5 of MDCO-216. Blood samples for this PK analysis of MDCO-216 concentration will be collected at the following time points: before infusion (0 min), 30 min, 2 h (at end of infusion), 4 h, 6 h, 12 h,
24 h and 168 h post commencement of infusion. Additionally, a pre-infusion PK sample will be collected at Dose 2, Dose 3 and Dose 4 to determine trough levels for MDCO-216 treatment.

Pharmacokinetic assessments of MDCO-216 will include Cmax, t1/2, Vd, Cl, AUC0-24, and AUCinf.
Formation of anti-MDCO-216 antibodies (ADA) will be assessed prior to each infusion dose and at Day 59.

The independent Data Monitoring Committee (DMC) will review safety data after the first 24 subjects receive infusion 2 of MDCO-216 or placebo.

An interim analysis for safety and efficacy will be performed and reviewed by the DMC after approximately 40 randomized subjects (33% of the anticipated total completers for MDCO-216 and placebo groups) complete the Treatment Phase to end of trial (EOT) visit (Day 59). Another
interim analysis for safety and efficacy may be performed and reviewed by the DMC after approximately 80 randomized subjects (66% of the anticipated total completers for MDCO-216 and placebo groups) complete the Treatment Phase to EOT visit (Day 59). A recommendation
may be taken to stop the study at either of these reviews.

All eligible subjects will be randomized and receive the initial administration of a single IV infusion of MDCO-216 or placebo within 14 days of the qualifying IVUS and following review of local post-angiography BUN and liver function tests (LFTs). The infusion will be stopped if a
clinically significant change in vital signs or electrocardiogram (ECG), or an infusion reaction, as determined by the investigator, occurs.

After each study drug administration, the subject will be observed in the clinic for at least four hours post infusion stop time and then discharged, except for the first 24 subjects who will remain in the clinic for 24 hours after the first, second and fifth infusions for additional safety observation.

Pharmacodynamics assessments will measure the effects of MDCO-216 on total and free cholesterol, triglycerides, and level of apolipoproteins [A-I, A-II, B].
Approximately one week (seven days) following the 5th (final) IV infusion, the subject will undergo the final limited angiogram and IVUS procedure.
End of treatment (EOT) evaluations will be conducted at the EOT visit (Day 59).

The expected duration of the subjects* involvement in the study will be up to 75 days, which includes screening and clinically indicated coronary angiogram, baseline IVUS, randomization, study drug administration, the course of five infusions, follow-up coronary angiogram and IVUS examination, and a 30 day follow-up period.

Study burden and risks

At this time the safety profile of MDCO-216 is not yet established. MDCO-216 has been previously tested in animals where there were no significant safety findings. In the previous study in healthy volunteers and patients with heart disease, 32 subjects received MDCO-216 and 16 subjects received placebo. In this study the drug was well tolerated with no serious adverse events. The most common adverse events seen were headache and fatigue. Other adverse events included nausea, diarrhea, dry mouth, abdominal distension, clot in a deep vein and frequent urination. Transient increase of lipase and amylase, with no symptoms were seen in 3 subjects treated with MDCO-216 and 2 subjects who received placebo.
A related product, known as ETC-216, which was studied before MDCO-216, has been tested in humans and allergic reactions were seen in several patients. In one study a patient had a reaction that may have been related to the drug and consequently died. MDCO-216 is produced by a new manufacturing process and allergic reactions of the type seen with ETC-216 were not seen with MDCO-216 when tested in animals and humans.

It is not known whether multiple infusions of MDCO-216 20 mg/kg will have a therapeutic benefit for subjects in the study in terms of cardiovascular outcome. The related product, ETC-216 study data suggested that at doses of 15 mg/kg and 45 mg/kg there was regression of atherosclerosis as measured by IVUS parameters

Risks Associated with the IV Line: The cannula can be painful and may cause a bruise. IV lines are usually safe and well tolerated and complications (problems) are rare, but can include infusion site reaction (redness, swelling), phlebitis (inflammation of the vein) and infection. The IV may come out accidentally or blood may leak around the line. If the IV is not in the vein, medication or fluid can be infused into their tissues, and can be associated with swelling, discomfort and irritation of the tissues. Rarely, a clot can develop in the IV line itself.
Risks associated with Intravascular Ultrasound (IVUS) and Coronary Angiogram Procedures: Some complications that may occur include, but are not limited to, oozing of blood around the catheter site, collection of blood (hematoma) under the skin, allergic reaction to the dye used during angiography that can occur during or following the procedure, or formation of a blood clot at the site of catheter insertion that might obstruct the circulation or cause injury to the blood vessel. Damage to parts of the body supplied by the artery could result in loss of function or amputation, or could upset your heart condition and its

symptoms. Local nerve damage, infection, irregularities of the heartbeat, stroke, heart attack or death may also occur. Complications that may occur with IVUS include, but are not limited to, transient spasm (sudden involuntary contraction of muscle in the wall of a blood vessel, which can severely narrow the vessel), dissection (separation of the layers of the walls of a blood vessel) or abrupt closure of a blood vessel, which could result in death.
Risks associated with Radiation: The cardiac catheterization (coronary angiogram) and IVUS procedures involve exposure to radiation which may increase risk of getting cancer. The amount of radiation exposure you will receive from the cardiac catheterization procedure has an estimated increased risk of 0.15%. The amount of radiation exposure received from an IVUS procedure has an estimated increase risk of 0.3%.

Reproductive Risks: The effects of MDCO-216 on the unborn child are unknown. It is not known if MDCO-216 could affect male sperm. There is no information on the long-term effects of MDCO-216 on fertility.

Contacts

Public
Medicines Company

Sylvan Way 8
07054 Parsippany
US
Scientific
Medicines Company

Sylvan Way 8
07054 Parsippany
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1)Male or female subjects * 18 years of age.
2)Have experienced a recent Acute Coronary Syndrome (ACS) event within 14 days of screening that requires a clinically indicated coronary angiogram.
3)A qualifying ACS event will be defined as follows:
A diagnosis of a qualifying MI event will be defined by abnormal levels of cardiac biomarkers (troponin I or T or CK-MB mass) with at least one determination greater than the 99th percentile or upper limits of normal for the laboratory and at least one of the following:;*Chest discomfort or symptoms of myocardial ischemia (* 10 minutes) at rest within 24 hours prior to hospitalization for MI.;*New ECG findings (or presumed new if no prior ECG available) indicative of acute myocardial ischemia in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB) as listed:;oNew or presumed new ST depression greater than 0.5 mm in 2 contiguous leads or T wave inversion greater than 1mm in leads with predominant R wave or R/S greater than 1 in 2 contiguous leads.;oNew or presumed new ST elevation at the J point in * 2 contiguous leads with the cut-off points: * 0.2 mV in men or * 0.15mV in women in leads V2-V3 and/or *0.1 mV in other leads or new or presumed new LBBB.;oNew tall R wave > 40 ms in V1, V2 and R/S * 1 in V1 with concordant positive T-wave in the absence of a conduction defect.;oNew Q waves * 30 ms wide and > 1mm deep in any 2 leads of a contiguous lead grouping or Q wave > 20ms or QS complex in leads V2 and V3 (These criteria also apply to silent MI detected during a routine follow-up visit).;oLoss of viable myocardium based on imaging evidence of new or presumed new wall motion or perfusion deficit (eg, echocardiography, left ventriculography during cardiac catheterization radionuclide angiography, single-photon emission tomography, MRI).;4)Baseline coronary angiogram must meet all of the following criteria for IVUS interrogation of TARGET ARTERY:;*Must be accessible to the IVUS catheter.;*Must have a stenotic area of * 20% and < 50% in lumen diameter by angiographic visual estimation within the length of the native coronary artery (*target segment*) for imaging by IVUS.;*The target artery has not undergone prior percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG).;*The target artery is not currently a candidate for intervention or a likely candidate for intervention over the treatment phase of the study and until the second IVUS interrogation at Day 36.;*The target artery may not be a bypass graft.;*The target artery may not be the culprit vessel for a previous MI.;*TARGET ARTERY MAY HAVE:;oA lesion of up to 60% stenosis, distal to the target segment, provided that this area is not a target for PCI or CABG.;oA single branch of the *target vessel* may have a narrowing * 70% by visual estimation, provided that the branch in question is not a target for PCI or CABG.;5)Willing and able to give informed consent before initiation of any study-related procedures and willing to comply with all required study procedures.

Exclusion criteria

1) Baseline IVUS not completed due to non-qualifying coronary angiogram as demonstrated by:
a) Greater than 50% reduction in lumen of the left main coronary artery by visual estimation.
b)Extensive CAD with no target vessel for IVUS interrogation.
2) Baseline IVUS interrogation determined to be unacceptable by the Atherosclerosis Imaging Core Laboratory (AICL).
3) Previous STEMI within the last 90 days (not including qualifying ACS event)
4) Clinically significant heart disease which, in the opinion of the Investigator, is likely to require CABG, PCI cardiac transplantation, surgical or percutaneous valve repair and/or replacement following index IVUS imaging (does not apply to PCI that occurs as a result of initial screening angiogram and completed prior to index IVUS imaging).
5) New York Heart Failure Association (NYHA) class III or IV heart failure or last known left ventricular ejection fraction less than 30%.
6)Coronary artery bypass surgery < 6 weeks prior to the qualifying IVUS.
7)Cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication.
8)Uncontrolled severe hypertension: systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg prior to randomization despite anti-hypertensive therapy.
9)Poorly controlled diabetes mellitus and an HbA1c greater than 10.0% prior to randomization.
10)Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver OR alanine aminotransferase (ALT), aspartate aminotransferase (AST), elevation greater 2x ULN OR total bilirubin elevation greater than 1.5x ULN at screening confirmed by a repeat measurement at least one week apart.
11)Fasting triglyceride value > 400 mg/dL.
12)Impaired kidney function defined as calculated glomerular filtration rate < 60 mL/min by eGFR. In addition, subjects with a 0.3 mg/dL or 25% increase in serum creatinine in the initial 3-5 days following angiography will be excluded from the study.
13)Serious comorbid disease in which the life expectancy of the subject is shorter than the duration of the trial (eg, acute systemic infection, cancer, or other serious illnesses). This includes all cancers with the exception of treated basal-cell carcinoma occurring > 3 years before screening.
14)Body weight > 120 kg.
15)Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least two methods of contraception (oral contraceptives, barrier methods, approved contraceptive implant, long- term injectable contraception, intrauterine device or tubal litigation). Women who are > 2 years postmenopausal defined as * 1 year since last menstrual period AND if less than 55 years old with a negative pregnancy test within 24 hours of randomization or surgically sterile are exempt from this exclusion.
16)Males who are unwilling to use an acceptable method of birth control during the entire study period (ie, condom with spermicide).
17)Previous participation in this study or any preceding study with ETC-216, MDCO-216, or similar investigational medicines containing ApoA-I proteins.
18)Known allergy to the phospholipid or any other component of the investigational product

(dimeric rApoA-IM, POPC, or mannitol and sucrose in phosphate buffer)
19)Treatment with other investigational medicinal products or devices within 30 days orfivehalf*lives, whichever is longer.
20)Known history of alcohol and/or drug abuse.
21)Use of other investigational medicinal products or devices during the course of the study, excluding Post-Marketing Registries.
22)Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:
a)Inappropriate for this study, including subjects who are unable to communicate or to cooperate with the investigator.
b)Unable to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study (including subjects whose cooperation is doubtful due to drug abuse or alcohol dependency).
c)Unlikely to comply with the protocol requirements, instructions and study-related restrictions (eg, uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study).
d)Have any medical or surgical condition, which in the opinion of the investigator would put the subject at increased risk from participating in the study.
e)Involved or a relative of someone directly involved in the conduct of the study.

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:	Recruitment stopped
Start date (anticipated):	09-05-2016
Enrollment:	29
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MDCO-216
Generic name:	rApoA-IM

Ethics review

Approved WMO Date:	17-11-2015
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	22-02-2016
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	01-04-2016
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 25286
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2015-000826-13-NL
CCMO	NL54240.094.15
OMON	NL-OMON25286