Investigational New Drug

MILANO PILOT

MDCO-216 Infusions Leading to changes in Atherosclerosis: a Novel therapy in development to improve cardiovascular Outcomes – Proof of concept IVUS, Lipids and Other surrogate biomarkers Trial

MDCO-216

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.

Protocol No.: MDCO-APO-15-01
EuDRACT No.: 2015-000826-13
PROTOCOL VERSION: Amendment #1

Drug Development Phase: IIA
Sponsor: The Medicines Company
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Issue Date: Date: 09 June 2015

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## PROCEDURES IN CASE OF EMERGENCY

### Emergency Contact Information

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*http://www.themedicinescompany.com/page/Global%20Medical%20Information
# PROTOCOL SYNOPSIS

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<td>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 (ACS).</td>
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<td>A multi-center, multi-national study of 120 subjects performed in approximately 20-30 centers</td>
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<tr>
<td><strong>Principal Investigator:</strong></td>
<td>Prof. Stephen Nicholls, MBBS PhD</td>
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## Study Period:

The estimated study period will be approximately 1 year from first subject enrolled to last subject completed.

### Objectives:

**Primary Objective**

To evaluate the effect of MDCO-216 treatment on the change in percent atheroma volume (PAV) of a target coronary artery as measured by intravascular ultrasound (IVUS) imaging following five weekly infusions of MDCO-216 in subjects with a recent acute coronary syndrome.

**Secondary Objectives**

- To evaluate the effect of MDCO-216 on the following additional atheroma parameters measured by IVUS:
  - change in total atheroma volume (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, an reduction in PAV) and an additional analysis of those with more than two standard deviations of the test/re-test variability.

**Safety Objectives**

- To evaluate the safety profile of MDCO-216.

**Exploratory Objectives**

- To evaluate the effects of MDCO-216 on lipids, lipoproteins, apolipoproteins and markers of HDL function such as cholesterol efflux and pre-beta 1 HDL.
- To explore the relationship between changes in plasma biomarkers (eg, cholesterol efflux) and changes in IVUS and other imaging parameters.
- To explore the pharmacokinetics (PK) of MDCO-216 after single and multiple doses in a subgroup of subjects.
- To explore the effect of MDCO-216 on composition of plaque on a subset of subjects in sites with appropriate imaging capabilities.
Methodology: 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 $C_{\text{max}}$, $t_{1/2}$, $V_d$, CI, $AUC_{0-24}$, and $AUC_{\text{inf}}$.

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.

Number of Subjects: Planned enrollment is 120 subjects to ensure that approximately 50 subjects in the MDCO-216 dose group and 50 subjects in placebo are available for analysis, allowing for a 15%-20% dropout rate. Twenty four subjects will participate in the PK substudy.

Diagnosis and Main Criteria for Selection:

Inclusion Criteria

Subjects may be included if they meet all of the following inclusion criteria prior to
randomization:

1) Male or female subjects ≥ 18 years of age.
2) Have experienced a recent 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:
     - New 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.
     - New 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.
     - New 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.
     - New Q waves ≥ 30 ms wide and >1 mm 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).
     - Loss 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:
     - A lesion of up to 60% stenosis, distal to the target segment, provided that this area is not a target for PCI or CABG.
     - A 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

Subjects will be excluded from the study if any of the following exclusion criteria apply prior to randomization:

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 angiography 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 < 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 > 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 > 2x ULN OR total bilirubin elevation > 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 or five half-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.

**Test Product, Dose and Mode of Administration**, MDCO-216 (20mg/kg) will be administered as an IV 360 mL infusion over two hours on Days 1, 8, 15, 22, and 29.

**Duration of Treatment:**
Two-hour IV infusion of MDCO-216 or placebo at five separate visits
Treatment Phase for each subject is up to 75 days (from screening through the EOT follow-up visit) for each randomized subject in a dose cohort, listed as follows:

- a. Screening: Day -14 to -1
- b. Randomization, initiation of Study Drug: Day 1
- c. Treatment Phase: Day 8, 15, 22 and 29
- d. Follow up IVUS: Day 36
- e. EOT follow-up visit: Day 59

**Reference Therapy, Dose and Mode of Administration:** Placebo (360 mL of 0.9% w/v NaCl) will be administered as an IV infusion over two hours on Days 1, 8, 15, 22, and 29.

**Criteria for Evaluation:**

**Efficacy:**

**Primary Endpoint**
- Change in PAV from baseline to Day 36 post-randomization, as determined by IVUS.

**Secondary Endpoints**
- 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.
- Proportion of subjects in each group with regression of coronary atherosclerosis, defined as reduction in PAV from baseline to Day 36 of more than two standard deviations of the test/re-test 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 (ie, any reduction in PAV).

**Exploratory Endpoints**
- Changes in features of plaque composition by IVUS imaging on a subset of subjects in centers that have the capability to perform Near Infra Red Spectroscopy (NIRS).
The effects of MDCO-216 on lipids, lipoproteins, apolipoproteins and markers of HDL function such as cholesterol efflux and pre-beta 1 HDL.

Full PK profiling will be performed in 12 subjects from the first 24 subjects who are enrolled and treated with MDCO-216 at select sites with the capabilities to meet the detailed PK requirements.

Anti-MDCO-216 antibodies (ADA) after multiple dose administration.

### Safety:
Adverse events (AEs), serious adverse events (SAEs), vital signs, ECG assessments, and clinical laboratory values (hematology, coagulation, chemistry, and urinalysis) will be collected from consent through the EOT visit (Day 59).

### Pharmacokinetic Assessments:
Pharmacokinetic assessments of MDCO-216 will include $C_{\text{max}}$, $t_{1/2}$, $V_{d}$, $Cl$, $AUC_{0-24}$, and $AUC_{\text{inf}}$.

### Pharmacodynamics:
Pharmacodynamics assessments will measure the effects of MDCO-216 on cholesterol efflux assays, levels of lipids and apolipoproteins (A-I, A-II, B).

### Sample Size and Power

Approximately 120 subjects will be randomized to two groups (one active dose group [MDCO-216 20 mg/kg], one control group [placebo]) in a ratio of 1:1. Sample size and power were estimated via t-test to determine the probability of detecting a significant result (active dose compared to the control group). Assuming zero change in PAV in the placebo group and a decrease in PAV in the treated groups by 1.5% (common standard deviation of 3.0), 50 subjects in the MDCO-216 dose group with evaluable baseline and follow-up IVUS data will provide approximately 70% power to detect a significant difference compared to the control group of 50 subjects at two-sided overall Type I error ($\alpha$) of 0.05 with two interim analyses. Assuming a dropout rate of 15%-20%, approximately 60 subjects will be randomized to the MDCO-216 group and 60 subjects to the placebo group, for a total randomized population of 120 subjects.

### Primary Endpoint Analysis:
The primary endpoint is defined as change from baseline to study end (Day 36 post-randomization) in coronary PAV as determined by IVUS. Analysis of covariance (ANCOVA) will be used to compare the change in PAV for compared to the control. The model will include change in PAV as the response variable, baseline PAV as the covariate, and dose group as factor, adjusting for country and previous statin use. Least square means, differences in least square means, and standard error compared to control will be reported.

### Secondary Endpoint Analysis:
The secondary endpoints of change in normalized TAV, change in TAV for the 10 mm most diseased segment, and the laboratory data will be analyzed using the same method described above for the primary endpoint. The results will be reported as adjusted means (LSMean ± standard error) and associated confidence intervals.

The proportion of subjects in each group with atheroma regression (PAV change <0) will be estimated with a 95% confidence interval according to binomial distribution. The groups will be compared for significance in difference in the proportion of subjects with atheroma regression using a Chi-squared test. The proportion of subjects in each group with atheroma regression greater than two standard deviations (2SD) of test-retest measurement variability (PAV change < - 2SD) will be analyzed similarly.

All other study-collected data will be analyzed descriptively and/or displayed graphically according to dose level. However, when appropriate, p-values and two-sided 95% confidence intervals may be estimated.
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<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>2SD</td>
<td>2 standard deviations</td>
</tr>
<tr>
<td>ABCA1</td>
<td>ATP-binding cassette, sub-family A, member 1</td>
</tr>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
</tr>
<tr>
<td>ADA</td>
<td>anti-drug antibody</td>
</tr>
<tr>
<td>ADR</td>
<td>adverse drug reaction(s)</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event(s)</td>
</tr>
<tr>
<td>AESI</td>
<td>adverse event of special interest</td>
</tr>
<tr>
<td>AICL</td>
<td>Atherosclerosis Imaging Core Laboratory</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>analysis of covariance</td>
</tr>
<tr>
<td>AP</td>
<td>alkaline phosphatase</td>
</tr>
<tr>
<td>ApoA-I</td>
<td>apolipoprotein A-I</td>
</tr>
<tr>
<td>ApoA-IM</td>
<td>apolipoprotein A-I Milano</td>
</tr>
<tr>
<td>aPTT</td>
<td>activated partial thromboplastin time</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the curve</td>
</tr>
<tr>
<td>AUC_{inf}</td>
<td>area under the curve of the serum concentration to infinity</td>
</tr>
<tr>
<td>BUN</td>
<td>blood urea nitrogen</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass graft</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>Cl</td>
<td>Clearance</td>
</tr>
<tr>
<td>C_{max}</td>
<td>maximum concentration</td>
</tr>
<tr>
<td>CPK</td>
<td>Creatine phosphokinase</td>
</tr>
<tr>
<td>CS</td>
<td>clinically significant</td>
</tr>
<tr>
<td>DCF</td>
<td>data clarification forms</td>
</tr>
<tr>
<td>DMC</td>
<td>data monitoring committee</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>eCRF</td>
<td>electronic case record form</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>EDC</td>
<td>electronic data capture</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>EOT</td>
<td>end of trial</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration of the United States</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>GGT</td>
<td>gamma glutamyl transferase</td>
</tr>
<tr>
<td>GOT</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>GPT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>GPV</td>
<td>Global Pharmacovigilance</td>
</tr>
<tr>
<td>HCP</td>
<td>host cell protein</td>
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</tbody>
</table>
HDL  high density lipoprotein
HDL-C high density lipoprotein-cholesterol
hr hour(s)
ICH International Conference on Harmonisation
IL-6 interleukin-6
INR international normalized ratio
IRB Institutional Review Board
ITT Intent-to-treat
IV intravenous
IVRS/IWRS interactive voice response system / interactive web response system
IVUS intravascular ultrasound
kg kilogram(s)
LBBB Left bundle branch block
LDH lactate dehydrogenase
LDL low density lipoprotein
LFTs liver function tests
LVH left ventricular hypertrophy
MDCO The Medicines Company
MDCO-216 recombinant ApoA-I Milano/Phospholipid complex – investigational medicinal product
MedDRA Medical Dictionary for Regulatory Activities
mg milligram(s)
MI myocardial infarction
Min minute(s)
mITT modified intent-to-treat
mL milliliter(s)
mm millimeter(s)
mmHg millimeters of mercury
NCS not clinically significant
NIRS Near Infra-Red Spectroscopy
NOAEL no observable adverse effect level
NYHA New York Heart Failure Association
PAV percent atheroma volume
PCI percutaneous coronary intervention
PCS potentially clinically significant
PD pharmacodynamic(s)
PI Principal Investigator
PK pharmacokinetic(s)
POPC 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine
PP per-protocol
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>PT</td>
<td>prothrombin time</td>
</tr>
<tr>
<td>rApoA-IM</td>
<td>recombinant Apo A-I Milano</td>
</tr>
<tr>
<td>RBC</td>
<td>red blood count</td>
</tr>
<tr>
<td>RCT</td>
<td>reverse cholesterol transport</td>
</tr>
<tr>
<td>SAD</td>
<td>single-ascending dose</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SAER</td>
<td>serious adverse event report</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SOP</td>
<td>standard operating procedure</td>
</tr>
<tr>
<td>SRO</td>
<td>Statistical Report Organization</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-segment elevation myocardial infarction</td>
</tr>
<tr>
<td>TAV</td>
<td>total atheroma volume</td>
</tr>
<tr>
<td>t1/2</td>
<td>terminal half-life</td>
</tr>
<tr>
<td>TEAE</td>
<td>treatment emergent adverse event</td>
</tr>
<tr>
<td>TNF-α</td>
<td>tumor necrosis factor-α</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>Vd</td>
<td>volume of distribution</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood count</td>
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</tbody>
</table>
1. INTRODUCTION

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.

MDCO-216 is a pre-β-like high-density lipoprotein (HDL) particle composed of a dimer of recombinantly produced human ApoA-I Milano (ApoA-IM), a naturally-occurring genetic variant of apolipoprotein A-I (ApoA-I), the key protein component of HDL, complexed to the phospholipid 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC). 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.

MDCO-216 had a predecessor compound known as either ETC-216 or ET-000216 while under development by Esperion Therapeutics and Pfizer, Inc. ETC-216 and MDCO-216 are comprised of the same components (recombinant human ApoA-IM/POPC) but MDCO-216 is manufactured using an improved process resulting in reduced host cell protein (HCP) contamination. Clinical studies that were under development by Pfizer, Inc. are referred to with the prefix A764. ETC-216 was studied in three completed clinical trials (one completed Phase I study and one completed Phase II study; one terminated Phase II study), comprising 97 subjects in total (see Section 1.2.2.1).

A recent Phase I study was conducted to assess the safety, tolerability, PK, and pharmacodynamics (PD) of ascending doses of MDCO-216 manufactured by the new process in healthy volunteers and subjects with known stable CAD. In this study, MDCO-216 was generally well tolerated with no serious adverse events (SAEs), deaths, or withdrawals. Apo A1 and pre-beta 1 HDL were increased in a dose-dependent manner and other parameters such as high density lipoprotein-cholesterol (HDL-C) and triglyceride showed the expected changes. ATP-binding cassette, sbu-family A, member 1 (ABCA1) cholesterol efflux was profoundly increased.

1.1. Background

Atherosclerotic vascular disease, including CAD, is the primary cause of morbidity and mortality in the western world. Prospective studies have linked CAD to three major modifiable factors: smoking, elevated blood pressure, and lipid abnormalities. Among the latter, a low HDL-C level has been implicated as a significant risk factor. The HDL particle is thought to protect arteries from atherosclerosis by transporting cholesterol and other lipids from the vessel wall into the bloodstream and subsequently delivering them to the liver for
elimination, a process called reverse cholesterol transport (RCT) [Zhang et al, 2003]. The key protein component of HDL is ApoA-I.

A genetic variant of ApoA-I, apolipoprotein A-I Milano (ApoA-IM), has been identified in approximately 40 individuals in a small village in northern Italy. The carriers are all heterozygous and are apparently protected from the development of atherosclerosis despite HDL-C concentrations in the lowest 5th percentile (10 to 30 mg/dL) and low ApoA-I concentrations [Gualandri et al, 1985]. In contrast to the pronounced macrovascular changes found in subjects with low HDL-C in the general population, there are no signs of premature atherosclerosis in the carriers of ApoA-IM [Sirtori et al, 2001].

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. Published literature describing a variety of animal models suggests that intravenous (IV) infusion of natural and synthetic HDL-mimetic complexes may have therapeutic utility in the: (i) prevention and regression of atherosclerosis, (ii) reduction of macrophage content in atherosclerotic plaques, (iii) reduction of thrombosis and platelet aggregation, and (iv) reduction of proliferation in response to mechanical injury to arteries [Ameli et al, 1994; Shah et al, 1998; Shah et al, 2001; Chiesa et al, 2002; Parolini et al, 2008 ]. Therefore, IV administration of MDCO-216 may have therapeutic benefit for the treatment of subjects with CAD and other forms of cardiovascular disease.

Intravascular ultrasound (IVUS) uses high frequency ultrasound to produce an image of the coronary lumen and the structure of the vessel wall. It enables precise measurement of the lumen area, as well as atheroma size and distribution, because it visualizes the entire vessel wall. The ability of IVUS to directly visualize atheroma in the vessel wall that are not detected by coronary angiography and to provide a cross-sectional image facilitates early diagnosis and treatment with the potential to significantly affect the prognosis of subjects with CAD.

Intravascular ultrasound (IVUS) was selected to assess coronary artery atheroma burden because of the high sensitivity of this imaging method compared to coronary angiography [Nissen et al, 2004; Nissen et al, 2008].

The current trial will study subjects who have had a recent ACS. This study will evaluate the effect of 20 mg/kg of IV MDCO-216 compared with placebo given over five weekly infusions on coronary artery atheroma burden assessed by changes in the percent atheroma volume (PAV) and the total atheroma volume (TAV), as measured by IVUS imaging. The study will also assess whether or not MDCO-216 is associated with regression of PAV.

1.2. MDCO-216

MDCO-216 is a macromolecular complex consisting of a dimer of the recombinant protein, rApoA-IM, and the phospholipid, POPC. The formulation currently also consists of sucrose and mannitol in phosphate buffer and is isotonic. MDCO-216 is stored frozen at -20°C until ready for use.

The nomenclature used to describe the components of the complex is as follows:

- Protein Intermediate: dimeric rApoA-IM;
Critical raw material: POPC;

Excipients: sucrose and mannitol in phosphate buffer;

Bulk MDCO-216 drug product: bulk solution of rApoA-IM (dimeric) complexed with POPC in phosphate buffer with mannitol, obtained in-situ after homogenization.


For more information on MDCO-216, see the Investigator’s Brochure (Edition 3 dated March, 2015).

1.2.1. Nonclinical Studies

Nonclinical studies conducted with MDCO-216 are extensively described in the Investigator’s Brochure (Edition 3 dated March, 2015).

In summary, 2-week and 6-week toxicology studies were performed in monkeys with MDCO-216. MDCO-216 was well tolerated in rats and monkeys and did not exhibit dose-limiting toxicities at 600 mg/kg and 300 mg/kg, the highest doses administered to each species, respectively. The no observable adverse effect level (NOAEL) for repeat dose studies in rats was 200 mg/kg. Higher doses were associated with minor changes in hematologic parameters that were not associated with organ-specific toxicity. Similar to the observations in rats, monkeys exhibited minor hematologic changes that were not considered to be of toxicologic significance. The NOAEL in monkeys was considered to be at least 300 mg/kg.

In addition, a human ex vivo whole blood assay was developed to monitor the stimulation of pro-inflammatory cytokines by MDCO-216 comparing product manufactured by the original and by the new process. The results indicated that MDCO-216 yields a product that does not appear to stimulate a pro-inflammatory cytokine response.

The overall toxicology data supported dosing of MDCO-216 in humans in this Phase IIa multiple-dose study of subjects with a recent ACS. Specifically, the 2-week and 6-week toxicology studies in cynomolgus monkeys demonstrated that MDCO-216 has an improved safety profile related to the reduced overall level of contaminating HCP compared to ETC-216. Moreover, the proposed starting dose of 5.0 mg/kg in the Phase I study provided adequate safety margins of 6.0 and 19 based on a NOAEL of 200 mg/kg from repeat dose and NOAEL of 600 mg/kg from single dose toxicology studies in the rat, respectively.

1.2.2. Clinical Studies

1.2.2.1. Previous Clinical Trials with ETC-216

MDCO-216 had a predecessor compound that was manufactured under the designations ETC-216 and ET-000216 when under development by Esperion Therapeutics and Pfizer, Inc., respectively. Both ETC-216 and ET-000216 are referred to as ETC-216. ETC-216 was manufactured by a different process than MDCO-216 leading to a level of HCP impurities that were associated with adverse safety findings in a clinical study.
ETC-216 was studied in three clinical trials: one Phase I, single-ascending-dose study, ETC-216-001 in 32 healthy volunteers and two multiple-dose Phase II studies, ETC-216-002 and A7641006, in 57 and 8 patients respectively, with ACS.

Single ETC-216 doses of up to 100 mg/kg were generally well tolerated in the Phase I study, ETC-216-001.

The Phase II study ETC-216-002 demonstrated that IV infusions of ETC-216 administered five times at weekly intervals produced significant regression of coronary atherosclerosis as measured by intravenous ultrasound [Nissen et al. 2003]. Two patients in Study ETC-216-002 experienced SAEs leading to their withdrawal from the study. One patient developed an elevated aspartate aminotransferase level accompanied by nausea, vomiting, and cholelithiasis. The second patient experienced an infusion reaction consisting of chills, nausea, diaphoresis, rigors, vomiting, and a mild rash.

In the Phase II Study A7641006, one patient experienced a hypersensitivity reaction followed by hypotension, stent occlusion, myocardial infarction, and cardiogenic shock, leading to multi-organ failure and death. Due to this SAE, enrollment in the study was suspended and the study was ultimately terminated. Upon subsequent analysis of the drug product, residual HCPs were identified and suspected to be linked to the SAE by inducing cytokine release, particularly IL-6, and eliciting a hypersensitivity reaction.

Because of the significant regression of coronary atherosclerosis seen in ACS patients in Study ETC-216-002, an optimized quality/manufacturing process was developed for MDCO-216. MDCO-216 has been shown to not elicit a pro-inflammatory cytokine response both in a repeat-dose nonclinical toxicology study in cynomolgus monkeys and ex vivo experiments with human whole blood. In contrast, ETC-216 from the lot that was administered to the patient who experienced the hypersensitivity reaction stimulated the release of IL-6 in the ex vivo whole blood assay.

1.2.2.2. Clinical Trials with MDCO-216

A Phase I single ascending dose (SAD) study (TMC-APO-11-01) examined the safety, tolerability, PK, and PD of MDCO-216 in healthy volunteers and subjects with known stable coronary artery disease. MDCO-216, in both healthy volunteers and subjects with stable CAD, was well tolerated up to doses of 40 mg/kg with no SAEs or other clinically significant safety findings. Pharmacodynamic changes included profound increases in ABCA1 efflux, apo AI and pre-beta-1 HDL.

The planned dose in this study will be 20 mg/kg which is lower than the highest dose tested in both an earlier Phase II study (ETC-216-002, Esperion Therapeutics) and the MDCO-216 SAD study. The earlier Phase II study measured percent and TAV reduction in coronary arteries using IVUS and found no additional efficacy in terms of atheroma volume reduction when comparing two dose groups, 15 mg/kg and 45 mg/kg. Therefore, testing MDCO-216 20 mg/kg in Phase IIa is believed to be an appropriate dose for this study based on previous preclinical and clinical experience with the compound.

This Phase IIa study will assess imaging parameters, efficacy, pharmacokinetic (PK), safety, and tolerability parameters with five weekly infusions of 20 mg/kg of MDCO-216. For additional information refer to the Investigator’s Brochure (Version 3 dated March, 2015).
The characterization of the imaging and PD and PK profile of MDCO-216 in subjects with CAD will provide initial data prior to a further study which will be performed to optimize dose selection for subsequent Phase III and other studies.

1.2.3. Known and Potential Risks and Benefits

MDCO-216 and its predecessor compound ETC-216 have been studied previously in various nonclinical and clinical studies. The predecessor compound of MDCO-216 (ETC-216) was manufactured by the original process and has been associated with safety findings due to the presence of contaminating HCP. MDCO-216 is manufactured by the current process and expected to have an improved safety profile due to the significant reduction in the level of contaminating HCP as demonstrated by additional release testing (improved HCP assay and assay for residual flagellin) in non-clinical toxicology studies as well as in ex vivo experiments with human whole blood.

The Phase I SAD study (TMC-APO-11-01) was designed to assess and confirm the safety, tolerability, PK, and PD of MDCO-216 in healthy volunteers and subjects with stable CAD. Appropriate safety measures and assessments were put in place to allow selection of a suitable dose range for Phase II. Doses up to 40 mg/kg were well tolerated in both healthy volunteers and subjects with stable CAD, with no SAEs or other clinically significant safety observations.

Clinical trials with new drugs generally bear the risk that there may be effects that are currently unknown and unforeseeable. Therefore, a thorough monitoring of possible adverse events (AEs) such as cytokine responses or antibody formation against MDCO-216 was conducted in study TMC-APO-11-01. There were no positive findings based on this monitoring.

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 but a previous study using ETC-216 suggested that at doses of 15 mg/kg and 45 mg/kg there was regression of atherosclerosis as measured by IVUS parameters.

In this study, a Data Monitoring Committee (DMC) will be established to monitor safety, including AEs, available laboratory parameters (cytokines, clinical chemistry, hematology, and urinalysis), vital signs, and electrocardiograms (ECGs). This committee will also assess efficacy and safety parameters at two interim assessments after 40 and 80 subjects have completed the treatment phase of the study.

On the basis of all data available to date, the conduct of the study is regarded as justifiable at the planned dose. This clinical trial will be a Phase IIa study in subjects with a recent ACS. Five IV infusions of MDCO-216 or placebo, as determined by randomization will be administered over two hours at one-week intervals. The duration of treatment administration (2 hours) was chosen based on tolerability data obtained in earlier clinical trials, which demonstrated a higher incidence of AEs with higher infusion rates. The results of previous studies with ETC-216 suggested that MDCO-216 should not be infused faster than at a rate of approximately 1.25 mg/kg/min. The maximum dose in this study is 20 mg/kg, corresponding to an infusion rate of 0.17 mg/kg/min.
The study will be conducted in compliance with the protocol, the principles of Good Clinical Practice (GCP), and applicable regulatory requirements.

1.3. Study Rationale

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. In previous clinical studies, the predecessor compound of MDCO-216 (ETC-216) has demonstrated the capability to decrease plaque volume in subjects with coronary atherosclerotic plaques. However, ETC-216 was associated with AEs in subjects with ACS, which proved to be related to impurities in the final drug product and has resulted in another manufacturing process to avoid this. The more advanced method consisted of using quadruple knock-out E. coli as biologic source coupled with sophisticated purification techniques. The significant changes in the manufacturing process of MDCO-216 have led to an improved safety profile in non-clinical toxicology studies. Also, it has been shown that blood of human subjects who responded to in vitro challenging with ETC-216 was devoid of such a reaction when challenged with MDCO-216.

Since the manufacturing process has changed significantly to eliminate contaminant HCPs, in the recent Phase I SAD study MDCO-216 was first tested in healthy volunteers before being administered to subjects with known CAD. The conservative dose escalation with substantial testing of inflammatory reactions, both ex vivo prior to administration and post dose, minimized the risk for the subjects. The extensive characterization of the manufacturing process resulting in strongly reduced levels of contaminating HCPs, and the improved safety profile in non-clinical toxicology studies make it highly unlikely that inflammatory reactions, previously associated with ETC-216, will occur in this trial. The rationale for performing this phase IIA study in subjects with a recent ACS is based upon the following considerations. After completing the healthy volunteer cohorts in the recent Phase I study, subjects with stable CAD were also included. No safety concerns were raised in a dose range up to 40mg/kg in both healthy volunteers and subjects. It is therefore unlikely that the proposed population of subjects with a recent ACS, will differ from subjects with stable CAD in terms of safety findings and are expected to be of a similar demographic profile. Therefore, it is expected that the significant manufacturing changes that resulted in an improved and acceptable safety profile in a relevant target population (CAD) for the product justifies further development of MDCO-216 in subjects with atherosclerosis and a recent ACS to regress plaque burden.

1.4. Study Population

The study population will consist of male and female subjects ≥ 18 years of age with CAD who are undergoing a clinically indicated coronary angiogram. Randomization and initiation of study drug treatment will not occur until a subject has met all inclusion and exclusion criteria.
2. **TRIAL OBJECTIVES AND PURPOSE**

2.1. **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.

2.2. **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.

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

2.4. **Exploratory Objectives**
- To evaluate the effects of MDCO-216 on lipids, lipoproteins, apolipoproteins and markers of HDL function such as cholesterol efflux and pre-beta 1 HDL.
- To explore the relationship between changes in plasma biomarkers (eg, cholesterol efflux) and changes in IVUS and other imaging parameters.
- To explore the pharmacokinetics (PK) of MDCO-216 after single and multiple doses in a subgroup of subjects.
- To explore the effect of MDCO-216 on composition of plaque on a subset of subjects in sites with appropriate imaging capabilities.
3. **TRIAL DESIGN**

### 3.1. Type/Design of Trial

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.

### 3.1.1. Study Details

The study will consist of 120 subjects across two groups, MDCO-216 20 mg/kg and a placebo group. Informed consent will be obtained from subjects meeting the inclusion/exclusion criteria before the initiation of any study-specific procedures. Subjects meeting angiographic criteria will undergo baseline IVUS imaging. Following IVUS acceptability by the IVUS Atherosclerosis Imaging Core Lab, eligible subjects will be randomized to receive MDCO-216 or placebo in a 1:1 treatment allocation ratio. Each subject will receive five IV infusions of blinded study drug on Days 1, 8, 15, 22, and 29.

Subjects will be stratified at randomization by country and for previous statin use so that approximately equal numbers of statin-treated and statin-naïve subjects prior to the recent ACS are randomized into the treatment groups.

The following study visits will occur in all subjects: Screening, Randomization, Days 1, 8, 15, 22, 29 (dosing), final IVUS Day 36 and the end of treatment (EOT) Day 59. Formation of anti-MDCO-216 antibodies (ADA) will be assessed prior to each infusion dose and at Day 59.

On Days 1, 8, 15, 22, and 29, investigational product infusions will be given. Safety will be evaluated by monitoring AEs, clinical laboratory evaluations, ECGs, and vital signs.

The final infusion will be given on Day 29 with the follow-up IVUS being performed on Day 36 and final in-person visit on Day 59.

The independent DMC will review safety data after the first 24 subjects have received the second infusion of MDCO-216 or placebo.
An interim analysis will be performed by the DMC after approximately 40 randomized subjects (33% completers for MDCO-216 and placebo groups) complete the Treatment Phase of the study. Another interim analysis may be performed by the DMC after approximately 80 randomized subjects (66% completers for MDCO-216 and placebo groups) complete the Treatment Phase of the study. These will be reviews of safety and efficacy. A recommendation may be taken to amend the study design or conduct.

3.1.2. PK Substudy

The first twenty-four subjects who are enrolled and randomized in the study (approximately 12 in each dose group), at selected sites with the capabilities to meet the detailed PK requirements, including in patient stay for 24 hours for multiple blood samples and observation, will undergo extensive blood sampling for potential PK analysis and in-patient stay for 24 hours for safety monitoring after the first two and the final infusions. They will also undergo an in-patient stay of 24 hours after the fifth infusion for PK sampling. The purpose of this PK sub-study is to evaluate PK parameters after single (Infusion 1) and multiple (Infusion 5) administrations of MDCO-216. Analysis will only be performed on subjects receiving MDCO-216.

Blood samples for analysis of MDCO-216 concentration will be collected at the following time points: before infusion (0 min), 30 minutes after commencement of infusion, 2 h (at end of infusion), 4 h, 6 h, 12 h, 24 h and 168 h after commencement of infusion. Pharmacokinetic assessments of MDCO-216 will include C_{\text{max}}, t_{1/2}, V_d, Cl, AUC_{0-24}, and AUC_{\text{inf}}.

3.2. Schematic Diagram of Trial Design

An overall schematic of trial design is shown in Figure 1.

Figure 1: Schematic of Overall Trial Design
3.3. **Primary Endpoint**

The primary endpoint 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:

\[
PAV \text{ (Week 6)} - PAV \text{ (baseline)}
\]

where *PAV is calculated as:*

\[
\frac{\sum (EEMCSA - LUMENCSA)}{\sum EEMCSA} \times 100
\]

EEMCSA is the cross-sectional area of the external elastic membrane and LUMENCSA is the cross-sectional area of the vessel lumen.

3.4. **Secondary Endpoints**

The secondary endpoints of this trial are:

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

  TAV is calculated as follows:

  First, the *average area of atheroma per cross-section for each subject is calculated as:*

  \[
  \frac{\sum (EEMCSA - LUMENCSA)}{n}
  \]

  Where EEMCSA is the cross-sectional area of the external elastic membrane, LUMENCSA is the cross-sectional area of the lumen, the difference is summed over the total anatomically comparable segment, and *n* is the number of cross-sections being measured for a subject.

  To compensate for differing lengths/number of cross-sections among subjects, TAV for each subject is normalized to a volume based on same number of cross-sections, (ie, calculated as the above average area of atheroma per cross-section multiplied by the median number of cross-sections measured for all study subjects in the modified intent to treat population).

  *The change in TAV is calculated as:*

  \[
  TAV \text{ (Day 36)} - TAV \text{ (baseline)}
  \]

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

  \[
  TAV_{10\text{ mm}} \text{ (D36)} - TAV_{10\text{ mm}} \text{ (baseline)}
  \]
Where TAV10 mm is the TAV in the most diseased segment. TAV10 mm is calculated as the sum of the differences between the external elastic membrane cross-sectional area and luminal cross-sectional area in the 10 mm most diseased segment at baseline:

\[ \sum (EEMCSA - LUMENCSA) \]

- 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.

3.5. Safety Endpoints

Safety will be evaluated through the EOT visit (Day 59) by monitoring AEs, SAEs, vital signs, ECG assessments, and clinical laboratory values (hematology, coagulation, chemistry, and urinalysis).

3.6. Exploratory Endpoints

The exploratory endpoints of this trial are:

- Changes in features of plaque composition by IVUS imaging on a subset of subjects in centers that have the capability to perform NIRS.
- The effects of MDCO-216 on PD parameters and biomarkers which may include but not limited to characterization of lipoprotein particles by 2D gel electrophoresis, determination of total and free cholesterol in different lipoprotein subsets.
- Full PK profiling will be performed in 12 subjects from the first 24 subjects who are enrolled and treated with MDCO-216 at select sites with the capabilities to meet the detailed PK requirements.
- Anti-MDCO-216 antibodies (ADA) after multiple dose administration.

3.7. Measures to Minimize/Avoid Bias

3.7.1. Blinded Study Where Pharmacist is Unblinded

The study will be conducted using a randomized, placebo-controlled, double-blind design. Specifics on how the blind for the study drug (MDCO-216 or placebo) is maintained, is provided in Section 5.3.

Allocation of treatment is not disclosed to the study team. Study medication will be prepared by the unblinded hospital pharmacist or designee and will be provided in such a way that the appearance, volume, and infusion rate is the same for all study groups to ensure that blinding will be maintained during the infusion. Pharmacists or designee will be required by signature
to keep the study personnel blinded. Furthermore, laboratory investigations will be done in a blinded fashion.

The randomization scheme will be generated and managed by an interactive voice response system / interactive web response system (IVRS/IWRS) system and overseen by designated unblinded personnel separated from the project team.

Unblinding is allowed for the laboratory performing the PK analysis in the 12 subjects who received MDCO-216 from the 24 subjects who underwent extensive PK sampling.

Unblinding is allowed for the DMC and if clinically relevant safety findings are observed the DMC will have to decide about recommendations for further study enrollment or protocol modification as defined in the DMC charter.
4. SUBJECT POPULATION

4.1. Number of Subjects

Approximately 120 subjects will be randomized in the study at global centers.

4.2. Inclusion Criteria

Subjects may be included in the study if they meet all of the following criteria prior to randomization:

1. Male or female subjects $\geq$ 18 years of age.
2. Have experienced a recent 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 ($\geq$ 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:
     - New or presumed new ST depression greater than 0.5 mm in 2 contiguous leads or T wave inversion greater than 1 mm in leads with predominant R wave or R/S greater than 1 in 2 contiguous leads.
     - New or presumed new ST elevation at the J point in $\geq$ 2 contiguous leads with the cut-off points: $\geq$ 0.2 mV in men or $\geq$ 0.15 mV in women in leads V2-V3 and/or $\geq$ 0.1 mV in other leads or new or presumed new LBBB.
     - New tall R wave $> 40$ ms in V1, V2 and R/S $\geq$ 1 in V1 with concordant positive T-wave in the absence of a conduction defect.
     - New Q waves $\geq$ 30 ms wide and $> 1$ mm deep in any 2 leads of a contiguous lead grouping or Q wave $> 20$ ms or QS complex in leads V2 and V3 (These criteria also apply to silent MI detected during a routine follow-up visit).
     - Loss 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 the following criteria for IVUS interrogation of Target Artery:
   - 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:
• A lesion of up to 60% stenosis, distal to the target segment, provided that this area is not a target for PCI or CABG.

• A 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.

4.3. Exclusion Criteria
Subjects will be excluded from the study if any of the following exclusion criteria apply prior to randomization:

1. Baseline IVUS not completed due to non-qualifying coronary angiogram as demonstrated by either of the following:
   • Greater than 50% reduction in lumen of the left main coronary artery by visual estimation.
   • 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 three months prior to randomization that is not controlled by medication.

8. Uncontrolled severe hypertension: systolic blood pressure > 180mmHg or diastolic blood pressure > 110mmHg prior to randomization despite anti-hypertensive therapy.

9. Poorly controlled diabetes mellitus and a 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 than 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 local 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 3-5 days following coronary 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 or five half-lives, whichever 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:

- Inappropriate for this study, including subjects who are unable to communicate or to cooperate with the Investigator.

- 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).

- 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).

- 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.

- Involved or is a relative of someone directly involved in the conduct of the study.

Subjects excluded for any of the above reasons may be re-screened for participation at any time if the exclusion characteristic has changed prior to time of randomization.

4.4. **Withdrawal Criteria**

All subjects have the right to withdraw at any point during treatment without prejudice. The investigator can discontinue any subject at any time if medically necessary. It will be documented whether or not each subject completed the clinical study. If for any subject study treatment or observations were discontinued, the reason will be recorded and the Sponsor should be notified promptly. Reasons that a subject may discontinue participation in a clinical study are considered to constitute one of the following:

- Adverse event(s)
- Death
- Subject withdrew consent
- Physician decision
- Lost to follow-up
- Infusion reaction (see Section 8.5)

It is imperative to obtain complete follow-up data for all subjects whether or not they receive their assigned treatment or have discontinued study drug. Every attempt should be made to collect follow-up information except for those subjects who specifically withdraw consent for release of such information. All procedures and laboratory specimens or tests requested for evaluation following administration of the Study Drug should be carried out when possible whether or not a subject continues to receive treatment according the protocol. Subjects will not be replaced in this trial.
4.4.1. **Withdrawal from Study Medication**

For any subject withdrawn from study medication, the expectation is that the subject will complete the following study visits unless the subject withdraws his/her consent:

- PK assessments relative to the last dose received, as applicable
- Final IVUS visit/assessment
- EOT visit/assessments

4.4.2. **Withdrawal from Trial**

For any subject who withdraws from the trial, the expectation is that the EOT assessments, including repeat IVUS examination are completed for subject safety, if the subject consents.
5. TREATMENT OF SUBJECTS

5.1. Study Medications

5.1.1. MDCO-216

For subjects randomized to active study drug, MDCO-216 will be administered as an IV 360 mL infusion for a duration of 2 hours on Days 1, 8, 15, 22, and 29 (see Pharmacy Manual for additional details).

All infusions will take place under medical supervision at a clinic or center with emergency and life-saving equipment available. The precise date and time of administration (start and end of infusion) will be captured on the case report forms.

5.1.2. Placebo (0.9% w/v NaCl)

To match MDCO-216 administration, for subject randomized to the placebo arm, a placebo infusion of 0.9% w/v NaCl will be administered as an IV infusion using the same volume (360 mL) and infusion time (2 hours). The precise date and time of administration (start and end of infusion) will be documented on the case report forms.

5.1.3. Packaging and Labeling

MDCO-216 will be provided by the Sponsor.

Medication labels will comply with regulatory requirements. The storage conditions for each medication provided will be described on the medication label.

Normal saline for placebo subjects will be taken from the site stock supply and is not provided by MDCO.

5.1.4. Storage

MDCO-216 will be stored in a secure freezer at a minimum temperature of minus 20°C at the appropriate conditions as specified in the Pharmacy Manual. Access should be strictly limited to the pharmacist and his/her designee. No other site staff will have access to study drug or study drug documentation to maintain blinding.

Neither the investigators nor any designees may provide Study Drug to any individual not participating in this protocol.

5.1.5. Study Drug Dispensing

Because MDCO-216 is stored at minus 20°C, the pharmacy will require 24 hours prior notice before study drug can be dispensed to allow adequate time for the product to thaw.

5.1.6. Accountability

The pharmacist or designee must maintain an inventory record of MDCO-216 received and all administered to assure the regulatory authorities and the Sponsor that the investigational new drug will not be dispensed to any person who is not a subject under the terms and
conditions set forth in this protocol. Drug accountability forms and/or specific instructions can be found in the Pharmacy Manual.

The MDCO-216 supplied for use in this study is to be prescribed only by the Principal Investigator or designated Sub-Investigators and may not be used for any purpose other than that outlined in this protocol.

During the study all used study drug containers (eg, empty vials/bottles) may be kept until the monitor has reviewed the accountability records.

All unused MDCO-216 will be returned to the Sponsor/designee or destroyed on site once the study drug has been inventoried and the monitor has reviewed the accountability records. In the event that MDCO-216 needs to be returned for any other reason, the site will receive a written request listing the drug lot number(s) to be returned and the reason for the return request.

5.1.7 Product Complaints

Sites are required to report any potential product safety or quality information to MDCO immediately but no later than 24 hours from the time of awareness, by phone or e-mail as follows:

United States of America: 1-888-977-6326
Europe: + (00) 80084363326 or + (00) 41448281084
All other geographies: (00) 41448281084
Email: Medical.information@themedco.com

Product complaints include, but are not limited to:

- Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, efficacy or purity of or performance of a MDCO medical device, drug or combination product.
- Any indication involving the possible failure of a distributed MDCO medical device, drug or combination product to meet any of its specifications.
- An indication that there is an unexpected physical change in the drug product such as discoloration.
- Change in shape of the drug product, presence of particulates or any other physical change that might affect the appearance and texture.
- An indication of contamination, a manufacturing defect or any other event that might indicate a compromise in product quality, stability, reliability, safety, effectiveness, performance or usage.
- An indication that the vial contains less than or more than its labeled concentration.
- An indication that there is an unexpected physical change in any part of the container (this includes the bottle, any part of the seal, the cap or the label).
- An indication that the product is mislabeled.
An indication that there is an unexpected physical change of the product or container once the product is diluted or reconstituted (the container includes the vial, bag, IV line, syringe or any other item that is in contact with the product.

- A falsification of the medicinal product

5.2. Concomitant Medications

5.2.1. Prohibited Concomitant Medications

Any investigational medicine other than the study drug will be prohibited for the duration of the study. Other HDL or Apo A1 based infusions are also prohibited.

5.2.2. Permitted Concomitant Medication(s)

Subjects eligible and enrolled are allowed to continue taking any clinically indicated medication for the treatment of existing conditions, including medications for recognized cardiovascular risk factors.

All contemporary evidence-based medical care for CAD and ACS should be initiated as early as possible in order to allow for stabilization of the treatment effects before randomization.

Investigators are encouraged to maintain background lipid modulating therapy (eg. statins, niacin, fish oil, bile acid sequestrants, dietary supplements) at doses as stable as possible throughout the study.

5.3. Blinding

5.3.1. Blinding of study medications

The study will be conducted using a placebo controlled, double-blind design. Since MDCO-216 is not completely visually indistinguishable from the placebo (0.9% w/v NaCl), an unblinded pharmacist or designee will prepare the study drug solutions and ensure that the infusion bags and IV lines are opaque or covered with opaque material (shrouds) to maintain the blind during infusion. If needed, Sponsor will provide materials.

The blinding will also be achieved by using labels on the investigational medicinal product, which does not allow for the identification of the true medication. More details can be found in the Pharmacy Manual.

5.3.1.1. In the event of an emergency - Unblinding

It is expected that the need for unblinding of a subject’s treatment will be rare. Every effort should be made to preserve the blind unless there is a compelling reason that knowledge of the specific treatment would alter the medical care of the subject. The investigator will attempt to contact the study MDCO MedInfo Hot Line prior to unblinding a subject’s treatment assignment, to discuss the clinical circumstances. Emergency unblinding for SAEs may be performed through the IVRS/IWRS. This option may be used ONLY if the subject’s acute well-being requires knowledge of the subject’s treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IVRS/IWRS. Any subject who is unblinded will be permanently discontinued from study therapy but should be...
continued in the study completing all study visits and procedures, including follow-up IVUS and all follow-up visits.

5.3.2. Method and Maintenance of Blinding

This is a randomized, placebo-controlled, double-blind study in which blinding of treatment assignment will be maintained throughout the conduct of the study.

The site pharmacist(s)/designee will be the only study team members at the site level who are unblinded to treatment assignment. To maintain blinding, direct contact between the unblinded staff and the blinded study team should be limited.

Randomized treatment will be assigned by an automated IVRS/IWRS. The blinding of treatment assignment will be maintained until the database is locked. Breaking of the blind for a specific subject will be considered only in the case where knowledge of the treatment assignment is deemed essential to subject safety or the occurrence of a SAE that, in the opinion of the investigator, cannot be adequately treated without knowing the identity of the study drug. Any intentional or unintentional breaking of the blind should be immediately reported to the Sponsor.

Each Principal Investigator and/or designee at the site will be provided with IVRS/IWRS instructions for subject unblinding (Section 5.3.1.1).

An unblinded team at the Sponsor level or their designee will be assigned as a resource to unblinded site personnel during the conduct of the study. This team may include unblinded Clinical Research Associates (CRAs) and unblinded Data Managers to monitor pharmacy records. Under no circumstances will the unblinded team discuss, share, or otherwise distribute any information that could potentially result in unblinding to anyone outside of the unblinded team.
6. SCHEDULE AND SEQUENCE OF PROCEDURES

This study consists of two periods:

1. Screening (Day -14 to -1) and randomization.
2. Treatment period (Days 1, 8, 15, 22, 29, follow-up IVUS [Day 36], and EOT [Day 59]).

The maximum duration of participation in the study will be up to 75 days.

**Screening and Randomization:**

The screening (baseline) period occurs prior to administration of study drug, following consent and consists of confirming eligibility and collecting baseline assessments. The Randomization (Day -1), and initiation of study drug (Day 1) will occur no more than 14 days following the baseline IVUS.

**Treatment Period:**

Dosing occurs on Days 1, 8, 15, 22 and 29. Subjects will not be discharged until after all blood draws and assessments have been completed and the required observation period has been completed.

**Dosing Days Observation – Subjects 1-24:**

The first 24 subjects are required to be observed for 24 hours post Dose 1 and Dose 2 of study drug. Observation for Dose 3 and 4 is a minimum of 4 hours. These subjects may also be participating in the PK sub-study and they will additionally follow the PK schedule of assessment and observation for 24 hours following Infusions #1 and #5. Following DMC review of the data from these subjects, the observation period for subsequently enrolled subjects may be reduced to 4 hours for all subjects and all doses.

**Dosing Days Observation – Subjects 25-120:**

Provided the DMC approves, subjects 25 and greater are required to be observed for a minimum of 4 hours following all doses of study drug.

**Treatment Period follow-up (Day 36 and Day 59):**

Follow up IVUS will be on Day 36 and final treatment period visit will occur on Day 59 (EOT Visit).

The Schedule of Events for the 12 subjects participating in PK assessments is presented in Table 1.

The Schedule of Events for subjects not participating in PK assessments is presented in Table 2.

The Schedule of blood sample collection times for PK Assessments is presented in Table 3.
### 6.1. Schedule of Events/Assessments

**Table 1: Schedule of Events for PK Subjects (12/24 subjects will undergo PK assessments)**

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Screening</th>
<th>Randomization</th>
<th>Infusion 1</th>
<th>Infusions</th>
<th>Final IVUS</th>
<th>End of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-14 to -1</td>
<td>-1</td>
<td>1&lt;sup&gt;12&lt;/sup&gt; (0-24 h)</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Physical Examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Randomization</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>12 Lead ECG&lt;sup&gt;2&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clinical labs&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Urinalysis&lt;sup&gt;4&lt;/sup&gt; (local)</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy test&lt;sup&gt;5&lt;/sup&gt; (local)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Screening</td>
<td>Randomization</td>
<td>Infusion 1 (0-24 h)</td>
<td>Infusions 2</td>
<td>Infusions 3</td>
<td>Infusions 4</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------</td>
<td>---------------</td>
<td>---------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Study Day</td>
<td>-14 to -1</td>
<td>-1</td>
<td>8 ± 1</td>
<td>15 ± 1</td>
<td>22 ± 1</td>
<td>29 ± 7</td>
</tr>
<tr>
<td>Cytokines</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anti-MDCO-216 antibodies</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>PK</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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<td>PD parameters</td>
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<td>X</td>
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<td>X</td>
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<td>Coronary Angiogram</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IVUS Examination</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Drug Administration</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant Medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>AE Reporting</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SAE Reporting</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

PK = pharmacokinetics; PD = pharmacodynamics; ECG = electrocardiogram; IVUS = intravascular ultrasound; US = ultrasound; AE = adverse event; SAE = serious adverse event

1. Vital signs: blood pressure, heart rate, temperature and respiration will be measured every 30 minutes during Study Drug Infusion and at 4 hours after completion of infusion. For Day 1,8 and Day 29 vital signs will be measured there after every 4 hours up to 24 hours.
2. ECG is administered prior to the infusion start.
3. Hematology, Chemistry, Coagulation will be performed prior to start of study drug start on infusion days (refer to Section 7.1.4 for details of lab tests).
4. Lab tests performed in participating institution’s laboratory.
5. Lab tests performed by study’s designated Central Lab facility.
6. Prior to infusion #1, any local lab results for serum creatinine, BUN and LFTs drawn within 3-5 days post angiogram should be reviewed. If none are available, these labs should be run locally and reviewed prior to the start of infusion #1. Analysis collection is to the infusion start.
7. Urinary analysis collection is prior to the infusion start.
Urine pregnancy test performed and results prior to the infusion start.

Lab Cytokine draws to be taken pre-dose and 4 hours after start of infusion. Anti-MDCO-216 antibodies draws to be taken prior to each infusion dose and at Day 59.

PD samples – Collected prior to each infusion and then at 2 and 4 hours after start of infusion. Refer to Section 7.2 for details of lab tests.

PK samples – Day 1 and Day 29 (0 hr [pre-infusion] and 30 min, 2 hr, 4 hr, 6 hr, 12 hr and 24 hr). All time points are calculated from infusion start time.

PK samples – Day 8, Day 15 and Day 22: 0 hr (pre-infusion) only. Refer to Table 3 for details.

Day 1 and Day 29 requires an overnight stay for at least 24 hrs to complete all PK/PD blood collections.

Follow-up angiogram will be limited to IVUS target vessel.

Submit request to Pharmacy 24 hours in advance of infusion time allow for sufficient time for the study drug to be thawed and prepared according to the Pharmacy Manual.
<table>
<thead>
<tr>
<th>Study Day</th>
<th>Screening</th>
<th>Randomization</th>
<th>Infusion 1</th>
<th>Infusions</th>
<th>Final IVUS</th>
<th>End of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>-14 to -1</td>
<td>-1</td>
<td>1&lt;sup&gt;1&lt;/sup&gt;</td>
<td>8</td>
<td>15</td>
<td>22</td>
<td>29&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0-24 h)</td>
<td>(± 1)</td>
<td>(± 1)</td>
<td>(± 1)</td>
<td>(± 1)</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>(± 1)</td>
<td>36</td>
<td>59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>59</td>
<td>(± 2)</td>
<td>(± 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Informed consent: X
- Medical History: X
- Physical Examination: X
- Inclusion/Exclusion Criteria: X X X
- Randomization: X
- Vital Signs<sup>1</sup>: X X X X X X X X
- 12 Lead ECG<sup>2</sup>: X X
- Clinical labs<sup>3</sup>: X X X X X X X X
- Urinalysis<sup>7</sup> (local): X X X X X X X X
- Pregnancy test<sup>7</sup> (local): X X X X X X X X
### Table 2: Schedule of Events for Subjects not participating in PK assessments (Continued)

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Screening</th>
<th>Randomization</th>
<th>Infusion 1</th>
<th>Infusions</th>
<th>Final IVUS</th>
<th>End of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1(\text{(0-24) h} )</td>
<td>2 (\pm 1)</td>
<td>3 (\pm 1)</td>
<td>4 (\pm 1)</td>
</tr>
<tr>
<td>Study Day</td>
<td>-14 to -1</td>
<td>-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytokines</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anti-MDCO-216 antibodies</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PD parameters</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Coronary Angiogram</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVUS Examination</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Drug Administration</td>
<td></td>
<td></td>
<td>X(\text{(12) h})</td>
<td>X(\text{(12) h})</td>
<td>X(\text{(12) h})</td>
<td>X(\text{(12) h})</td>
</tr>
<tr>
<td>Concomitant Medications</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>AE Reporting</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SAE Reporting</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

PK = pharmacokinetics; PD = pharmacodynamics; ECG = electrocardiogram; IVUS = intravascular ultrasound; US = ultrasound; AE = adverse event; SAE = serious adverse event

1 Vital signs: blood pressure, heart rate, temperature and respiration will be measured every 30 minutes during Study Drug Infusion and at 4 hours after completion of infusion. For Day 1,8 and Day 29 vital signs will be measured thereafter every 4 hours up to 24 hours.

2 ECG is administered prior to the infusion start.

3 Hematology, Chemistry, Coagulation will be performed prior to start of study drug start on infusion days (refer to Section 7.1.4 for details of lab tests).

4 Lab tests performed in participating institution’s laboratory.

5 Lab tests performed by study’s designated Central Lab facility.

6 Prior to infusion #1, any local lab results for serum creatinine, BUN and LFTs drawn within 3-5 days post angiogram should be reviewed. If none are available, these labs should be run locally and reviewed prior to the start of infusion #1. Analysis collection is prior to the infusion start.

7 Urinary analysis collection is prior to the infusion start.

8 Urine pregnancy test performed and results prior to the infusion start.

9 Lab Cytokine draws to be taken pre-dose and 4 hours after start of infusion. Anti-MDCO-216 antibodies draws to be taken prior to each infusion dose and at Day 59.
PD samples – Collected prior to each infusion and then at 2 and 4 hours after start of infusion. Refer to Section 7.2 for details of lab tests.

Day 1 and Day 29 requires an overnight stay for at least 24 hrs to complete all PK/PD blood collections.

Follow-up angiogram will be limited to IVUS target vessel.

Submit request to Pharmacy 24 hours in advance of infusion time allow for sufficient time for the study drug to be thawed and prepared according to the Pharmacy Manual.
Table 3: Schedule of Blood Sample Collection Times for PK Assessments

<table>
<thead>
<tr>
<th>Day</th>
<th>Day 8</th>
<th>Day 15</th>
<th>Day 22</th>
<th>Day 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>0 min</td>
<td>0 min</td>
<td>0 min</td>
<td>0 min</td>
</tr>
<tr>
<td>(± 10 min)</td>
<td>(± 10 min)</td>
<td>(± 10 min)</td>
<td>(± 10 min)</td>
<td>(± 10 min)</td>
</tr>
<tr>
<td>30 min (± 5 min)</td>
<td></td>
<td>30 min (± 5 min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 h (± 5 min)</td>
<td></td>
<td>2 h (± 5 min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 h (± 10 min)</td>
<td></td>
<td>4 h (± 10 min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 h (± 10 min)</td>
<td></td>
<td>6 h (± 10 min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 h (± 15 min)</td>
<td></td>
<td>12 h (± 15 min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h (± 30 min)</td>
<td></td>
<td>24 h (± 30 min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Day 36) 168h (± 4 hr)</td>
</tr>
</tbody>
</table>

Note: PK draw times are to be calculated from the infusion start time.
6.2. **General Conduct of the Trial**

Written informed consent will be obtained for this study by the Principal Investigator or designee from all subjects before the performance of any protocol-specific procedure. A separate consent will be obtained for the subjects in the PK sub-study.

6.3. **Screening Period (Up to 14 days prior to randomization)**

The following procedures will be performed within 14 days prior to randomization (See Section 7 for detailed tests required):

- Inclusion/Exclusion criteria review
- Informed Consent
- Chemistry
- Hematology
- Coagulation
- Urinalysis
- Demographic data
- Complete medical history
- Concomitant medication review
- Complete physical exam including vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- 12 lead ECG
- Pregnancy test, urine (when applicable)
- The screening coronary angiogram and IVUS will be completed and sent to AICL for review. The subject will not be randomized until the site has received confirmation of IVUS eligibility
- Recording of AEs and SAEs when they occur including monitoring for thrombotic events (see Section 8).

Randomization should only occur once eligibility is confirmed.

All screening laboratory tests will be performed in the participating institution’s laboratory. The results of all screening (liver function tests [LFTs]), serum amylase, serum lipase, HbA1c, creatinine (calculated glomerular filtration rate [GFR]) laboratory tests should be reviewed prior to administration of any protocol-required therapy. If the results confirm an exclusion criterion or suggest any contra-indication to MDCO-216 or placebo the subject will not be randomized.
6.4. Randomization (Day -14 to-1)

Randomization should only occur after:

- Review of AICL’s results of the subject’s qualifying IVUS
- Review of the inclusion/exclusion criteria
- Review of urinalysis, serum creatinine and BUN
- Pregnancy test, urine (when applicable)
- Investigator has determined that the subject is medically stable following the qualifying angiography and IVUS
- Recording of AEs and SAEs when they occur including monitoring for thrombotic events (see Section 8).

The site should document the date/time that the randomization occurred according to their local clock.

After the subject has been randomized and at least 24 hours prior to the Day 1 visit, a request should be made to the pharmacy for dispensation of study drug to allow sufficient time for the study drug to be thawed and prepared according to the Pharmacy Manual.

6.5. Initiation Of Study Drug Administration (Day 1)

Within 14 days following the date of the qualifying IVUS:

- Re-confirm inclusion/exclusion criteria
- Vital signs (sitting blood pressure, heart rate, temperature, and respiratory rate)
- Review/update of concomitant medication use
- The subject will receive MDCO-216 or placebo by IV infusion
- 12-lead ECGs
- Chemistry
- Hematology
- Coagulation
- Blood draws for anti-MDCO-216 antibodies
- In addition, if results of recent blood draws 3-5 days post angiography are not available blood draws will be performed for serum creatinine, BUN and LFTs by the site local laboratory and reviewed. Any subject with abnormal values will not receive initiation of dosing
- Blood draws for the PD analysis of MDCO-216 including fasting lipids and pre- and post-infusion cytokines
Blood draw for PK analysis for PK subjects according to the schedule in Table 3. These subjects will remain in the clinic at least for 24 hours to complete the scheduled blood draws.

- Urinalysis analyzed by the site local laboratory
- Pregnancy test (when applicable)
- Recording of AEs and SAEs when they occur including monitoring for thrombotic events (see Section 8)

### 6.6. Treatment Period Visits (Days 8, 15, 22)

At least 24 hours prior to each scheduled visit, the investigator must request that study drug be available from the pharmacy on the day of the visit.

The following procedures will be performed during the Treatment Period visit, prior to commencement of infusion:

- Review/update of concomitant medication use
- Vital signs (sitting blood pressure, heart rate, temperature, and respiration)
- Blood draw for PD markers including fasting lipids and pre- and post-infusion cytokines
- Blood draw for PK analysis according to the schedule in Table 3 for the PK subjects
- Blood draws for clinical chemistry, hematology and coagulation will be performed and sent to a central laboratory for analysis
- Blood draws for anti-MDCO-216 antibodies
- Urinalysis analyzed by the site local laboratory
- Pregnancy test (when applicable)
- Infusion of study drug
- Recording of AEs and SAEs when they occur including monitoring for thrombotic events (see Section 8)

The following will occur after each infusion:

- Blood draw for cytokine assessment
- Recording of AEs and SAEs when they occur including monitoring for thrombotic events (see Section 8)

### 6.7. Treatment Period Visit (Day 29)

At least 24 hours prior to each scheduled visit, the investigator must request that study drug be available from the pharmacy on the day of the visit.
The following procedures will be performed during the Treatment Period visit, prior to commencement of infusion:

- Review/update of concomitant medication use
- Vital signs (sitting blood pressure, heart rate, temperature, and respiration)
- Blood draw for PD markers including fasting lipids and pre- and post-dose cytokines
- Blood draw for PK analysis according to the schedule in Table 3 for the PK subjects. These subjects will remain in the clinic for 24 hours to complete the scheduled blood draws.
- Blood draws for clinical chemistry, hematology and coagulation will be performed and sent to a central laboratory for analysis
- Blood draws for anti-MDCO-216 antibodies
- Urinalysis analyzed by the site local laboratory
- Pregnancy test (when applicable)
- Infusion of study drug
- Recording of AEs and SAEs when they occur including monitoring for thrombotic events (see Section 8)

The following will occur after each infusion:

- Blood draw for cytokine assessment
- Recording of AEs and SAEs when they occur including monitoring for thrombotic events (see Section 8)

6.8. **Final IVUS Visit (Day 36)**

The following procedures will be performed during the IVUS Follow-Up visit:

- Review/update of concomitant medication use
- A 12-lead ECG
- Abbreviated physical exam including vital signs (sitting blood pressure, heart rate, temperature, and respiration)
- Blood draw for PD including fasting lipids and PK markers
- Blood draws for clinical chemistry, hematology and coagulation will be performed and sent to a central laboratory for analysis
- Urinalysis analyzed by the site local laboratory
- Limited coronary angiogram and final IVUS
- Recording of AEs and SAEs when they occur including monitoring for thrombotic events (see Section 8)
6.9. **End of Treatment (EOT) Phase Safety Visit (Day 59)**

The following procedures will be performed at the EOT phase of the study as a follow-up visit:

- Review/update of concomitant medication use
- A 12-lead ECG
- Blood draws for clinical chemistry, hematology and coagulation will be performed and sent to a central laboratory for analysis
- Blood draws for anti-MDCO-216 antibodies
- Urinalysis analyzed by the site local laboratory
- Pregnancy test (when applicable)
- Vital signs (sitting blood pressure, heart rate, temperature, respiration)
- Blood draw for PD markers including fasting lipids and cytokines
- Recording of AEs and SAEs when they occur including monitoring for thrombotic events (see Section 8)
7. PROTOCOL ASSESSMENTS

7.1. Assessment of Safety

7.1.1. Adverse Events

Subjects will be carefully monitored for adverse events (AEs) by the investigator during the designated study period including the screening and pre-randomization periods. The decision to release a subject from the clinic following dosing visits will be made by the investigator. For AEs occurring post discharge subjects will be instructed to contact the site and if needed will return to the clinic. All AEs and SAE information collected during the study, regardless of during or in-between clinic visits must be documented in source document/medical record and will be captured in the electronic case record form (eCRF).

Infusion reactions will be recorded as AEs of special interest as part of the eCRF and as detailed in the schedule of assessments.

Those events that fit the criteria of SAEs must be reported to MDCO in an expedited manner (see Section 8 for definitions and reporting requirements). Subjects experiencing AEs or abnormal test findings will be followed clinically until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator and Sponsor.

It is expected that the investigator will provide or arrange appropriate supportive care for the subject if necessary.

7.1.2. ECG Assessment

For assessment time points refer to Schedule of Events/Assessments.

A 12-lead ECG will be recorded after the subject has rested in supine position for at least five minutes.

The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether the findings are clinically relevant, whether changed from baseline, if abnormal, and whether the ECG changes constitute an adverse event.

The ECG on infusion Day 1 will be performed prior to infusion start.

7.1.3. Vital Signs Assessment

Vital signs will be captured per the Schedule of Events/Assessments and are comprised of the assessment of sitting systolic and diastolic blood pressure, heart rate respiratory rate and temperature. Assessments of vital signs resulting in clinically significant abnormal values will be repeated in order to exclude an erroneous assessment.

7.1.4. Laboratory Assessments

The following parameters will be determined at the Central Laboratory using validated standard methods according to the institutional laboratory standard operating procedure
(SOP). Each parameter that falls outside the normal range will be assigned as either H (high) or L (low) in comparison to the normal range. The investigator must interpret each “outside the normal range” value as not clinically significant (NCS) or clinically significant (CS). In the latter case the investigator must provide a comment describing the reason why the value is considered clinically significant and determine whether the laboratory finding constitutes an AE or an SAE. Additional laboratory assessments (BUN, creatinine and LFTs) will be performed at the investigator sites local laboratory to assess eligibility for study dug infusion. Details are provided in the schedule of assessments.

7.1.4.1. **Hematology**

For hematology parameters, a whole blood sample will be taken into an EDTA tube. For assessment time points refer to Schedule of Events/Assessments in Section 6.1.

- Hemoglobin
- Hematocrit
- Red blood count (RBC)
- White blood count (WBC) and differential cell count
- Platelets
- Reticulocyte count

7.1.4.2. **Clinical Chemistry**

For clinical chemistry parameters, a blood sample will be taken into a serum tube. For assessment time points refer to Schedule of Events /Assessments in Section 6.1. For cholesterol measurements, see Section 7.2 Assessment of Pharmacodynamics. Clinical chemistry will be reviewed by the investigator prior to commencement of each infusion of study medication.

- Serum Amylase, Serum Lipase, Plasma Glucose and Tryptase
- Total bilirubin (direct & indirect, if abnormal)
- BUN / Urea
- Uric acid
- Creatinine
- Total protein
- Alkaline phosphatase (AP)
- Aspartate aminotransferase (AST; GOT)
- Alanine aminotransferase (ALT; GPT)
- Gamma-Glutamyl transpeptidase (GGT)
- Lactate dehydrogenase (LDH)
- Creatine phosphokinase (CPK)
- Hb A1c (local; screening only)
- Sodium (Na+)
- Potassium (K+)
- Chloride (Cl-)
- Calcium (Ca2+)
- hs-CRP

7.1.4.3. Coagulation

For coagulation parameters, a blood sample will be taken into a plasma tube. For assessment time points refer to Schedule of Events / Assessments in Section 6.1.

- aPTT
- PT
- INR
- Fibrinogen

7.1.4.4. Urinalysis

Urinalysis will be performed and evaluated by dipstick analyses at the investigational site local lab. In case of abnormal results, microscopy and other assessments noted below will be performed at the local lab. For assessment time points refer to Schedule of Events/Assessments in Section 6.1.

Urinalysis will be performed from a sample of mid-stream urine. The following parameters will be assessed:

- Urinalysis (Stix): Nitrite, protein, glucose, ketone, urobilinogen, bilirubin, RBC/erythrocytes, WBC/leukocytes, pH, urine sediment (microscopic examination will be only performed in the event of abnormalities)

7.1.4.5. Cytokine Testing

Assays for cytokine IL6 and tumor necrosis factor-α (TNF-α) testing will be performed. For cytokine testing a blood sample will be taken into a plasma tube. For assessment time points refer to Schedule of Events / Assessments in Section 6.1.

7.1.4.6. Anti-MDCO-216

Assays for anti-MDCO-216 assessments will be conducted at Pharmaceutical Product Development Inc (PPD Inc) in Richmond, Virgina, USA. For anti-MDCO-216 assessments a blood sample will be taken into a serum tube. For assessment time points refer to Schedule of Events / Assessments in Section 6.1.
7.1.4.7. Pregnancy Testing

Urine pregnancy testing will be performed in women of child bearing potential. For assessment time points please refer to the Schedule of Events / Assessments in Section 6.1.

7.2. Assessment of Pharmacodynamics

7.2.1. Lipid Profile

Assays for lipid profile assessments will be conducted at a central laboratory. For assessment time points refer to “PD Parameters” in the Schedule of Events / Assessments in Section 6.1.

For the determination of lipid profile a fasting blood sample will be in an EDTA tube. Full details are provided in the laboratory manual.

7.2.2. Cholesterol Efflux

Assays for cholesterol efflux assessments will be conducted at Vascular Strategies in Plywood, USA at the end of the study. For time points refer to “PD Parameters” in the Schedule of Events / Assessments in Section 6.1. Full details are provided in the laboratory manual.

7.2.3. Other Pharmacodynamic Analyses

Please note that collected samples may be analyzed for additional parameters (eg, other lipids and lipoproteins, lipoprotein particle profile and pre β HDL) at laboratories to be defined to provide insight in the mechanism of action of MDCO-216. Samples may also be analyzed for markers of inflammation and cardiovascular risk. This does not require an amendment to the protocol. Full details are provided in the laboratory manual.

7.3. Assessment Of Coronary Angiography and IVUS

Subjects who have signed the informed consent form for IVUS should have the IVUS performed immediately following the angiography for the qualifying ACS event. Subjects who have a PCI as a result of the qualifying event angiography will have the baseline IVUS performed immediately following the PCI. Any intervention to the proposed target IVUS vessel will exclude this vessel from being used as the target IVUS vessel.

The accuracy and reproducibility of the IVUS endpoints of the study are dependent upon the Investigator’s commitment to rigorous image acquisition techniques. The AICL at the Cleveland Clinic will provide a separate IVUS guidance document to all participating sites. Adherence to these guidelines will ensure low observer variability and high quantitative imaging.

Ultrasound systems cannot be interchanged between baseline and follow-up time points. All imaging conditions performed at baseline time point must be duplicated at the follow-up time point.
All baseline angiographic studies must be forwarded to the AICL at the Cleveland Clinic. IVUS cases must be reviewed and approved by the AICL before subjects can be randomized to study treatment.

7.4. **Assessment of Pharmacokinetics**

Blood samples for the determination of MDCO-216 will be obtained at the time points specified in the Schedule of Assessments (Table 3).

Storage tubes and printed labels will be supplied by the analytical laboratory. Each individual’s samples will be stored as a package for that individual. Samples will be stored at $-20^\circ$C until shipment to the bioanalytical laboratory.

7.5. **Sample Collection Timing**

For PK sampling the predose blood draw may be taken any time within one hour before the start of the infusion. Samples taken after the start of infusion and on subsequent days should be taken within the time window specified in the Schedule of Assessments (Table 3).

In addition the actual times of all laboratory sample collection will be documented in the eCRF.
8. ADVERSE EVENTS

8.1. Definitions

8.1.1. Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Planned hospital admissions and/or surgical operations for an illness or disease that existed before the drug was given or the subject was randomized in a clinical study are not to be considered AEs.

Adverse events or abnormal test findings will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor/Investigator.

8.1.1.1. AE Severity

The severity of an AE will be assessed by the investigator. The investigator should ensure that any subject experiencing an AE receives appropriate medical support until the event resolves.

Adverse events (AE) will be graded on a 3-point scale and reported as indicated on the case report form. The intensity of an AE is defined as follows:

1 = Mild: Discomfort noticed, but no disruption to daily activity.
2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.
3 = Severe: Inability to work or perform normal daily activity.

8.1.1.2. Study Drug Causality

The relationship of an AE to study treatment will be assessed with consideration to the following criteria:

- Temporal relationship to the initiation of study medication
- Response of the event to withdrawal of study medication
- AE profile of concomitant therapies
- Clinical circumstances during which the AE occurred
- Subject’s clinical condition and medical history
Categorization of causality will be designated by the investigator as stated below:

1. **Unlikely related** - Lack of reasonable possibility of a causal relationship between the event and the IMP. This means that there are little to no facts (evidence) or arguments to suggest a causal relationship.

2. **Reasonable possibility** - Reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

### 8.1.2. Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening, i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred (it does not include an event that, had it occurred in a more severe form, might have caused death),
- Results in a significant, persistent or permanent change, impairment, damage or disruption in the subject's body function/structure, physical activities and/or quality of life,
- Requires in-subject hospitalization or prolongs hospitalization,
- Is a congenital anomaly/birth defect, or
- Is another medically significant event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., allergic bronchospasm requiring intensive treatment in an emergency department or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse).

A distinction should be drawn between serious and severe AEs. Severity is an estimate or measure of the intensity of an AE, while the criteria for serious AEs are indications of adverse subject outcomes for regulatory reporting purposes. A severe AE need not necessarily be considered serious and a serious AE need not be considered severe. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a MI that may be considered minor could also be an SAE if it prolonged hospitalization.

When death occurs with an SAE, the cause of death must be reported as an SAE. “Fatal” will be reported as the outcome for these events.

### 8.1.3. Medication Errors

Medication errors refer to any unintended error in the dosing or administration of the study product as per protocol.

Medication Errors generally fall into four categories as follows:
1. wrong medication
2. wrong dose (including dosing regimen/duration of infusion, strength, form, concentration, amount)
3. wrong route of administration
4. wrong patient (not administered to the intended patient)

Medication Errors include occurrences of overdose and underdose of the study product.

**Overdose:** Administration of a quantity of a medicinal product given per administration or per day which is above the maximum recommended dose according to the protocol for the investigational product as applicable. This also takes into account cumulative effects due to overdose.

**For this protocol, an overdose is defined as follows:**
An overall dose (mg/kg) load that is higher than the dose to be given in this study (ie, MDCO-216 at doses greater than 20 mg/kg).

**Underdose:** Administration of a quantity of a medicinal product given per administration or per day which is below the minimum recommended dose according to the protocol for the investigational product as applicable.

**For this protocol, an underdose is defined as follows:**
An overall dose (mg/kg) load that is lower than the dose to be given in this study, MDCO-216 20 mg/kg.

8.1.4. **AEs of Special Interest**
An AE of special interest (AESI); (serious or non-serious) is one of scientific and medical concern specific to the Sponsor’s product or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. See Section 8.5 for an AESI that has been identified for this study.

8.2. **Procedure for Non-Serious Adverse Event Recording**
All non-serious AEs that occur during the designated study period beginning after signing of informed consent and up to the EOT visit (Day 59) must be assessed and recorded on the source documents and eCRF, regardless of causal relationship to the study drug.

8.3. **Procedure for Serious Adverse Event Reporting**
All SAEs that occur during the designated study period beginning after signing of informed consent and up to the EOT visit (Day 59) must be reported to MDCO Global Pharmacovigilance Department (GPV) within 24 hours of awareness of the event using the provided study-specific SAE Report Form. The completion and processing of the SAE Report Form (paper or electronic) should be per the instructions in the provided SAE Report Form completion guidelines. In addition to completing the SAE Report Form, each SAE must be entered on the appropriate page of the eCRF.
The investigator must assess the causality for each SAE.

MDCO will contact the investigator, if necessary, to clarify any of the event information. The investigator should provide any follow-up information for the event to MDCO as soon as it becomes available.

If the investigator is notified of a SAE that occurs post-study period, that requires to be reported to the Sponsor (e.g., an event suspected to be causally related to study drug), the event should be reported through the process described above.

Where appropriate, if required by local regulations or procedures, the investigator should report these events to the Institutional Review Board (IRB)/Ethics Committee (EC) and/or national regulatory authority.

8.4. Procedure for Medication Error Reporting

Medication errors with or without an associated AE need to be recorded as medication errors in the eCRF as described in Section 8.2.

Medication errors with an associated SAE need to be recorded as medication errors and reported to MDCO GPV as described in Section 8.3.

A mis-dosing protocol deviation (refer to Section 12.3) would need to be reported as a medication error if it was an “unintended error” as defined in Section 8.1.3.

8.5. Procedure for Reporting AEs of Special Interest

The following AESI has been identified for the study product in this protocol. Non-serious AESIs should be reported to MDCO GPV within 72 hours and AESI should be reported within 24 hours as per reporting procedure provided in Section 8.3. The SAE/AESI form should be utilized but a serious outcome may not be selected if the AESI is not serious. The SAE report form should indicate that the reported event is an AESI. AESIs for this study product/protocol:

Infusion Reactions

Infusion reactions, usually occurring within four hours of the start of the infusion, may imply an immunologic basis, such as IgE-mediated reactions (anaphylaxis) or may be reactions that are not immunologically mediated, such as direct mast cell degranulation (anaphylactoid). These reactions are clinically identical, and require prompt, accurate assessment and astute management to alleviate symptoms, which may include but are not limited to rash, lung congestion, or, in some cases, life-threatening breathing difficulty and hypotension. These types of reactions will be captured as AEs/SAEs during the trial.

It is important to note that subjects who experience an infusion-related AE/SAE during the study drug administration will be discontinued from study treatment, but should not be discontinued from the clinical trial. Such subjects should continue in the clinical trial to ensure that follow-up occurs at the clinically appropriate intervals.
8.6. **Procedure for Reporting Pregnancies**

Occurrences of pregnancy in a study subject or study subject’s partner should be reported within 24 hours to MDCO GPV using the Pregnancy Reporting form. In cases where a pregnancy occurs with a SAE, the Serious Adverse Event reporting form should be used to report the SAE and the Pregnancy Reporting form should be used to report the pregnancy. When a pregnancy occurs without any concurrent SAE, the Pregnancy Reporting form may be submitted alone. The pregnancy must be followed through to outcome of pregnancy. Any pregnancy discovered from the time of consent to follow-up needs to be reported.
9. DATA COLLECTION

An electronic data capture (EDC) system will be used for this trial. All users will be trained on the technical features of the EDC as well as the content of the eCRF by qualified personnel prior to gaining access to the EDC. A User ID/Password will be granted after training. This ID is not to be shared amongst the study staff. All users must have a unique account to enter or review data. The eCRF should be filled out at the site within two days after each visit and within three days after the last visit. It is not expected that the eCRF will serve as source for any data collected in this trial. If there is a reason for a site to do so, it must be approved by MDCO and documented in the site files.

Prior to the database being locked, the investigator or designee will review, approve, and sign/date each completed eCRF corresponding to the blinded pages and the appropriate unblinded designee will similarly address the unblinded section of the eCRF. This signature serves as attestation of the Investigator’s responsibility for ensuring that all data entered into the eCRF are complete, accurate, and authentic. After the end of the trial, a copy of the data will be provided to the site. This copy will contain the final data, an audit trail of activity on the data, and any queries and answers that were posted for data clarification.
10. STATISTICAL PLAN

This is a 120 subject, placebo-controlled, double blind, randomized trial. Subjects will be recruited from approximately 20-30 global sites. Subjects that qualify for entry into the study will be randomly assigned in a 1:1 ratio to receive MDCO-216 20 mg/kg or placebo stratified by country and previous statin use. The objectives of this study are to evaluate the safety, tolerability, disease progression measures, and PD of MDCO-216 infusion with the intention to select an optimal dose for future studies. A separate Statistical Analysis Plan (SAP) document will provide more detailed specifications in data analysis and presentation.

10.1. Sample Size

Approximately 120 subjects will be enrolled into two groups: one active MDCO-216 dose group and the placebo control group in 1:1 ratio. Sample size was estimated using t-test to determine the power of detecting a significant result (active dose compared to the control group). Assuming zero change in percent atheroma volume (PAV) in the placebo group and decrease in PAV in the MDCO-216 group of -1.5 (common standard deviation of 3.0), 50 subjects in each group with evaluable baseline and follow-up IVUS data will provide approximately 70% power to detect a significant difference at two-sided overall Type I error (α) of 0.05 with two planned interim analyses. Accounting for an assumed dropout rate of 15%-20%, approximately 60 subjects will be enrolled into the MDCO-216 treatment group and 60 subjects in the placebo group, for a total randomized population of 120 subjects.

10.2. Randomization

Subjects will be randomized to MDCO-216 (20 mg/kg) or placebo. This will be in a 1:1 ratio. Randomization will be stratified by country and whether or not the subject is statin naïve (yes/no) prior to entering the trial.

Randomization should only occur once subject eligibility is confirmed. Subjects will be identified by their assigned randomization number.

10.3. General Statistical Considerations and Definitions

10.3.1. Analysis Populations

The following populations will be used for data analyses and/or presentation.

10.3.1.1. Intent-to-Treat (ITT) Population

All subjects randomized into the trial. Treatment classification will be based on the randomized treatment. This population will be used to assess the randomness of treatment allocation.
10.3.1.2. **Modified Intent-to-Treat (mITT) Population**

All randomized subjects who receive at least one dose of study drug and have both the baseline and follow-up IVUS assessment. Treatment classification will be based on the randomized treatment. This will be the primary population for analysis of the primary and secondary endpoints.

10.3.1.3. **Per-Protocol (PP) Population**

All mITT subjects who received all five infusions without major protocol violations. The PP population will be finalized during a blind data review before database lock. This will be the supportive population for analysis of the primary and secondary endpoints.

Detailed criteria for inclusion into the PP population will be described in the SAP.

10.3.1.4. **Pharmacokinetics (PK) Population**

All subjects who have any valid samples measured for study drug levels. This population will be used for PK analysis.

10.3.1.5. **Safety Population**

All subjects who received at least one dose of study drug. Treatment classification will be based on the actual treatment received. This will be primary population for the safety analyses.

10.3.2. **Missing Data Handling**

Unless otherwise specified, missing data will not be imputed and will be excluded from the associated analysis.

10.4. **Statistical Analyses**

10.4.1. **General Statistical Methods**

All study-collected data will be summarized by treatment group using descriptive statistics, graphs, and/or raw data listings. Categorical variables will be summarized using counts and percentages. Percentages are based on the number of subjects in the analysis set for whom there are non-missing data, unless otherwise specified. Continuous variables, including changes from baseline, will be summarized using descriptive statistics (n, mean, standard deviation [SD], median and interquartile range [Q1 and Q3], minimum and maximum).

Prior to database lock, a full SAP will be finalized which will describe in further detail the full planned analysis, analysis populations, observation periods, and special algorithms.

Statistical analyses will be carried out using SAS statistical analysis software version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina, USA).
10.4.2. Demographic and Background Characteristics

Subject demographics and baseline characteristics including medical history will be summarized by treatment group using the ITT, mITT, PP, and safety populations.

10.4.3. Study Drug and Concomitant Medications

Summary of each prior (pre-baseline) medication and concomitant (baseline or later) medication will be provided by treatment. Medications may not be coded with any standard dictionary. Subjects will be counted only once within each period by medication.

10.4.4. Efficacy Analysis

10.4.4.1. Primary Efficacy Endpoints

The primary endpoint is the change (change from baseline as EOT minus pre-treatment) in PAV in a targeted (imaged) coronary artery for all anatomically comparable slices (EOT and pre-treatment), as measured by IVUS. Change in PAV will be analyzed using analysis of covariance (ANCOVA). The model will include change in PAV as the response variable, baseline PAV as a covariate and treatment group as factor, adjusting for country and previous statin use. The difference in change from baseline between the treatment group and the placebo group will be reported and compared as adjusted means (LSMean ± standard error) with associated confidence intervals.

10.4.4.2. Secondary Efficacy Endpoints

The secondary endpoints of change in normalized total atheroma volume (TAV), change in TAV for the 10 mm most diseased segment and the laboratory data will be analyzed using the same method described above for the primary endpoint. The results will be reported as adjusted means (LSMean ± standard error) and associated confidence intervals.

The proportion of subjects in each group with atheroma regression (PAV change <0) will be estimated with a 95% confidence interval according to binomial distribution. The groups will be compared for significance in difference in the proportion of subjects with atheroma regression using a Chi-squared test. The proportion of subjects in each group with atheroma regression greater than 2 standard deviations of test-retest measurement variability (PAV change < - 2SD) will be analyzed similarly.

All other study-collected data will be analyzed descriptively and/or displayed graphically. However, when appropriate, p-values and two-sided 95% confidence intervals may be estimated.
10.4.5. Safety Analysis

10.4.5.1. Adverse Events

The MedDRA dictionary will be used for coding AEs classified as preferred term. An AE occurring on or after study treatment will be counted as a treatment emergent AE (TEAE).

The number (percentage) of subjects reporting TEAEs for each preferred term will be tabulated by system-organ class, by system-organ class and severity, and by system-organ class and relationship to study drug. If more than one event occurred with the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe or related occurrence for the summary by severity, or relationship to study drug, respectively.

When appropriate, p-values and two-sided 95% confidence intervals may be estimated.

10.4.5.2. Laboratory Tests

Clinical laboratory assessments for safety include hematology, clinical chemistry, coagulation, urinalysis, and anti-MDCO-216 antibodies. Absolute changes and percent changes from baseline in laboratory test values will be summarized by dose level at each time point. If applicable, analyses will also be performed by dose level for number and percent of subjects with laboratory values considered potentially clinically significant (PCS) as defined by the SAP.

10.4.5.3. Vital Signs

Change and percent change from baseline in vital signs will be summarized descriptively at each scheduled time point by treatment group. The number (percentage) of subjects with findings on physical examination will be summarized by treatment group.

10.5. Pharmacokinetic Parameters

Plasma concentration of MDCO-216 will be summarized descriptively. Graphical displays of mean (with standard deviation) concentrations versus time will be presented at each time point.

The following pharmacokinetic parameters will be estimated: area under the concentration versus time curve (AUC), maximum concentration (Cmax), terminal half-life (t1/2), clearance (Cl), and volume of distribution (Vd).

All pharmacokinetic parameters will be descriptively analyzed for the PK analysis set. Descriptive statistics comprise of N, mean, geometric mean, SD, median, % coefficient of variation (%CV), minimum and maximum.

10.6. Interim Analyses

An interim analysis of efficacy is planned during trial when the primary efficacy data from 33% of randomized subjects (approximately 20 MDCO-216 and 20 placebo and a total of 40) completed EOT visit (Day 59) are available. Another interim analysis will be
performed for the DMC review after approximately 80 randomized subjects (66% completers) have completed the Treatment Phase of the study to EOT visit (Day 59). DMC will review both efficacy and safety data from these interim analyses (Additional information provided in DMC Charter).

In case of early trial termination due to superiority in efficacy or futility, reference stopping boundaries based on O’Brien-Fleming alpha spending function will be used to control the overall type-I error at two-sided level of 0.05 (see Table 4). Adjusting for the efficacy interim analyses at 33% and 66% completed subjects the nominal $\alpha$ for final analysis is 0.0464.

<table>
<thead>
<tr>
<th>Percent of completed subjects</th>
<th>Critical value</th>
<th>Nominal alpha</th>
<th>Cumulative alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>33%</td>
<td>3.7307</td>
<td>0.0002</td>
<td>0.0002</td>
</tr>
<tr>
<td>66%</td>
<td>2.5262</td>
<td>0.0115</td>
<td>0.0116</td>
</tr>
<tr>
<td>100%</td>
<td>1.9917</td>
<td>0.0464</td>
<td>0.0500</td>
</tr>
</tbody>
</table>

Note: PASS software 12 was used to calculate the stopping boundary.

To minimize the potential of “operational biases”, a DMC charter is developed to guide the interim analysis conduct, communication, and decision-making process. The data monitoring process will be performed by an independent DMC, which is external to sponsor, and the interim efficacy analysis will be performed by an independent Statistical Report Organization (SRO). The rules of interim analysis and decision-making processes will be further specified in the DMC charter.
11. RECORDS RETENTION

Food and Drug Administration of the United States (FDA) regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- At least two years following the date on which a New Drug Application is approved by the FDA, or
- Two years after the Sponsor notifies the investigator that no further application is to be filed with the FDA.

Similarly, International Conference of Harmonisation (ICH) guidelines require that essential documents be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product.

To comply with these requirements, the investigator will not dispose of any records relevant to this study without either (1) written permission from the Sponsor or (2) providing an opportunity for the Sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study, including any data clarification forms (DCFs) received from the Sponsor. Such documentation is subject to inspection by the Sponsor or its agents, the FDA and/or other regulatory agencies.
12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Monitoring

The Sponsor has ethical, legal and scientific obligations to carefully follow this study in accordance with established research principles and applicable regulations. The investigator, as part of his responsibilities, is expected to cooperate with the Sponsor in ensuring that the study adheres to the protocol and GCP requirements.

As part of a concerted effort to fulfill these obligations, the Sponsor's monitor will visit the center(s) during the study in accordance with the Monitoring Plan set forth for this trial. The investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records/source documents to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

12.2. Auditing

The Sponsor may conduct audits at the study center(s). Audits will include, but not be limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to permit audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also inspect the investigator during or after the study. The investigator should contact the Sponsor immediately if this occurs, and must permit regulatory authority inspections.

12.3. Protocol Deviations

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the Sponsor, or their agent, at the earliest possible time by telephone. This will allow an early joint decision regarding the subject’s continuation in the study. The investigator and the Sponsor will document this decision. The IRB/EC will be informed of all protocol changes by the investigator in accordance with the IRB/EC established procedure. No deviations from the protocol of any type will be made without complying with all the IRB/EC established procedures.

The following will be classified as Protocol Deviations:

- 2-hour infusion not administered for any reason other than subject safety or withdrawal
- Mis-dosing including change in dosing regimen and duration*
  - Timing (+/- 30 min) of 2 hr requirement
Wrong dose (Dose concentration, wrong dose, wrong treatment)

- Missing scheduled infusion date unrelated to safety lab assessment
- Administration of first infusion when pre-dose local safety labs are not drawn or abnormal
- Final IVUS not performed for subjects with baseline IVUS for any reason other than subject safety or withdrawal
- Missed visit through Day 59 (EOT) visit
- Inclusion criteria violation
- Exclusion criteria violation
- Informed consent not signed and dated or signed and dated after any protocol-related procedures
- Unintentional un-blinding of the study treatment

*If the mis-dosing was unintended, (ie, a medication error), the error should be reported as per instructions in Section 8.4, Procedure for Medication Error Reporting*
13. **ETHICS AND RESPONSIBILITY**

This study will be conducted in compliance with the protocol, the Sponsor’s standard operating procedures and/or guidelines, FDA regulations, the ICH GCP guidelines, the Declaration of Helsinki, and other local regulations, as applicable.

13.1. **Informed Consent**

Written informed consent will be obtained from all subjects (or their guardian or legally authorized representative) before any study-related procedures (including any pre-treatment procedures) are performed. The investigator(s) has both ethical and legal responsibility to ensure that each subject (and their guardian or legally authorized representative) being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent form, which shall be approved by the same IRB or EC responsible for approval of this protocol. Each informed consent form shall include the elements required by ICH, Part E6, Section 4.8 and any applicable local regulations. The investigator agrees to obtain approval from the Sponsor of any written informed consent form used in the study, preferably prior to submission to the IRB or EC.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or a qualified designee) and it is felt that the subject understands the implications of participating, the subject and the investigator (or designee) shall sign the IRB- or EC-approved written informed consent form. The subject shall be given a copy of the signed informed consent form, and the original shall be filed appropriately, according to the institution. A second copy may be filed in the subject's medical record, if allowed by the institution.

13.2. **Institutional Review Board/Ethics Committee**

This protocol, the written informed consent form, and any materials presented to subjects shall be submitted to the IRB or EC identified with this responsibility. Notification in writing of approval must come from the IRB or EC chairman or secretary, to the investigator, either as a letter or as a copy of the appropriate section of the IRB or EC meeting minutes where this protocol and associated informed consent form were discussed. The investigator will not participate in the decision. If the investigator is an IRB or EC member, the written approval must indicate such non-participation in the voting session. The investigator will submit status reports to the IRB or EC as required by the governing body. The IRB or EC must be notified by the investigator in writing of the interruption and/or completion of the study; the investigator must promptly report to the IRB or EC all changes in research (protocol amendments) and will not make such changes without IRB or EC approval, except where necessary to eliminate apparent immediate hazards to human subjects. In cases where it is necessary to eliminate immediate hazards to subjects, the IRB or EC must then be notified of the change as per local requirements. The investigator is required to maintain an accurate and complete records of all written correspondence to and received from the IRB or EC and must agree to share all such documents and reports with the Sponsor.
13.3. Executive Committee

An Executive Committee consisting of academic experts who participated in the development of the protocol and/or will provide ongoing scientific and operational oversight to the study. The Executive Committee will monitor progress of study enrollment, make recommendations to the Sponsors based on the DMC recommendations, and oversee the presentation and publication of the trial results. The membership, roles and responsibilities of the Executive Committee are further described in the Executive Committee Charter.

13.4. Data Monitoring Committee (DMC)

An external independent DMC of experienced physicians and a statistician will formally review the accumulating data on a regular basis to ensure there is no avoidable increased risk for harm to subjects and make recommendations on future study conduct to the Executive Committee and Sponsor.

Serious AEs and other pre-defined significant safety parameters will be reviewed on a monthly basis. All other safety information will be reviewed at two monthly intervals. The first safety review will occur when 24 subjects have received two doses of MDCO-216 or placebo with subsequent full reviews after 40 and 80 subjects have completed the Treatment Phase of the study to Day 59. Timing for other periodic safety reviews will be specified in DMC Charter.

Following the completion of the treatment phase by the first 40 randomized subjects (33%), an interim analysis will be performed by the DMC for safety and efficacy with a recommendation being made to the Sponsor and Executive Committee regarding further conduct of the study. A subsequent interim analysis for efficacy and safety will occur, after 80 randomized subjects (66%) have completed the study to Day 59.

Additional reviews based upon recruitment may occur at the request of the DMC and ad hoc reviews may occur without the knowledge of the sponsor. DMC meetings will consist of an open and closed session. A member or members of the Sponsor and Executive Committee will attend the open sessions of the DMC meetings, but will not under any circumstances attend any of the closed sessions.

Following each DMC review the DMC chairman on behalf of the committee will provide a letter of recommendation to the sponsor regarding the continued conduct of the study. This letter may recommend study continuation as planned, amendments to the study design, additional analyses or assessments to be performed, or termination of the study.

Analyses for the DMC are provided by the Independent Statistical Center which is external to and independent from MDCO. The Independent Statistical Center will be provided with the randomization codes and provide unblinded data sets to the DMC for review in the closed sessions. A designated representative of the Independent Statistical Center will attend both the open and closed sessions of the DMC.

Full details will be provided in the DMC charter.
14. CONFIDENTIALITY

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. However, authorized regulatory officials and Sponsor personnel will be allowed full access to the records. All medications provided and subject bodily fluids and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

Only unique subject numbers in eCRFs will identify subjects. Their full names may, however, be made known to a product regulatory agency or other authorized official if necessary.

With respect to the clinical trial data that is received from countries in the European Economic Area and Switzerland, MDCO has certified adherence to the US-EU and the US-Swiss Safe Harbor Principles.
15. PUBLICATION AND COMMUNICATION OF STUDY RESULTS

On completion of the study it is anticipated that the study results will be submitted in a timely manner for publication in one or more peer-reviewed journals as well as presented at relevant scientific congresses. The Executive Committee will be responsible for the preparation of the primary manuscript, the Executive Committee and Sponsor will contribute in authoring publications and presentations of the study results. The Sponsor will be informed of any manuscript and provided the opportunity to review the materials to protect its intellectual property rights.

All reports and/or information, including all clinical data, will be the sole property of sponsor and will constitute confidential information of sponsor. Sponsor has the right to use information at its own discretion in press releases, company presentations, reports, company website, etc.
16. INVESTIGATOR AGREEMENT

I have read and understand the protocol (including the Investigator’s Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this study. I will personally conduct the study as described.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel responsible to me who will participate in the study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the investigational new drug MDCO-216, the concurrent medications, the efficacy and safety parameters, and the conduct of the study in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or Ethics Committee (EC) responsible for such matters in the Clinical Study Facility where MDCO-216 will be tested prior to commencement of this study. I agree to adhere strictly to the attached protocol. I understand that this IRB- or EC-approved protocol will be submitted to relevant regulatory authorities by the Sponsor, as appropriate. I agree that clinical data entered on case report forms by me and my staff will be utilized by the Sponsor in various ways such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow Sponsor monitors and auditors full access to all medical records/source documents at the research facility for subjects screened or randomized in the study.

I agree to provide all subjects with informed consent forms, as required by government and ICH regulations. I further agree to report to the Sponsor any adverse experiences in accordance with the terms of this protocol, ICH guideline, Part E6, Section 4.11 and applicable local regulations.

________________________________________  _______________________________
Principal Investigator (Signature)  Date

________________________________________
Principal Investigator (Printed Name)

________________________________________
Institution Name
17. REFERENCES


