AHA PRESENTATION  STATISTICAL ANALYSIS PLAN

-AHA Late Breaking Analysis

Version 0.1

September 9, 2016
Protocol Number: MDCO-APO-15-01

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.
TABLE OF CONTENTS

1. TRIAL INTRODUCTION ................................................................................. 4
   Schematic Diagram of Trial Design ................................................................. 4
2. OBJECTIVES AND STUDY DESIGN ............................................................. 9
   2.1. Primary Objectives .................................................................................. 9
   2.2. Secondary Objectives ............................................................................. 9
   2.3. Safety Objectives .................................................................................. 9
   2.4. Exploratory Objectives ......................................................................... 9
3. ANALYSIS POPULATIONS .......................................................................... 10
   3.1 Intent-to-Treat (ITT) Population ............................................................... 10
   3.2 Modified Intent-to-Treat (mITT) Population ............................................... 10
   3.3 Safety Population ................................................................................... 10
4. ANALYSIS ENDPOINTS ............................................................................ 11
   4.1. Primary Endpoint .................................................................................. 11
   4.2. Secondary Endpoints ............................................................................. 11
   4.3. Safety Endpoints .................................................................................. 12
5. STATISTICAL ANALYSES ......................................................................... 13
   5.1. General Statistical Methods ................................................................. 13
   5.2. Subject Disposition and Study Completion .............................................. 13
   5.3. Demographics and Baseline Characteristics .......................................... 13
   5.4. Prior and Concomitant Medication ......................................................... 13
   5.5. Efficacy Analysis .................................................................................. 14
       5.7.1 Primary Efficacy Endpoints ............................................................... 14
       5.7.2 Secondary Efficacy Endpoints ........................................................... 14
   5.8 Safety Analyses ...................................................................................... 15
       5.8.1 Adverse Events .............................................................................. 15
       5.8.5 Laboratory Assessments ................................................................. 15
   5.9. Assessment of Pharmacodynamics ....................................................... 16
       5.9.1 Lipid Profile ................................................................................... 16
   5.10. Assessment of Coronary Angiography and IVUS ............................... 16
7. COMPUTER METHODS .................................................................................. 18
8. CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL ................. 19
REFERENCES ................................................................................................. 20
1. TRIAL INTRODUCTION

This analysis plan provides a description of the strategy, rationale, and statistical methodology to be used to assess the interim results for the MDCO-APO-15-01 trial after obtaining data for approximately 126 patients. The purpose of the AHA presentation Statistical Analysis Plan is to pre-specify the endpoints to be analyzed and the statistical approaches and processes to the pre-defined analyses of the study data.

MDCO-APO-15-01 is 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.

This study is 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 weekly IV infusions of blinded study drug.

This statistical plan describes the details for an analysis for safety and efficacy that will be presented at the 2016 AHA after approximately 126 randomized subjects complete the Treatment Phase to end of trial (EOT) visit (Day 59). 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 ACS 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.

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 (about 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 (days 29-59).

Schematic Diagram of Trial Design

An overall schematic of trial design is shown in Figure 1.
Figure 1: Schematic of Overall Trial Design

Schedule of Events/Assessments

Table 1: Schedule of Events for Subjects included in the AHA analysis

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Scree ning</th>
<th>Randomiz ation</th>
<th>Infusion 1</th>
<th>Infusions</th>
<th>Final IVUS</th>
<th>End of Treatmen t</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 (0-24 h)</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>-14 to -1</td>
<td>X</td>
<td></td>
<td></td>
<td>(± 1)</td>
<td>(± 1)</td>
<td>(± 1)</td>
</tr>
<tr>
<td>-1</td>
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<td></td>
<td>2</td>
<td>15</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>Study Day</td>
<td>Screening</td>
<td>Randomization</td>
<td>Infusion 1</td>
<td>Infusions</td>
<td>Final IVUS</td>
<td>End of Treatment</td>
</tr>
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<td>------------</td>
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<td>------------</td>
<td>-----------</td>
<td>------------</td>
<td>------------------</td>
</tr>
<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>8 (± 1)</td>
<td>15 (± 1)</td>
<td>22 (± 1)</td>
</tr>
<tr>
<td>Inclusion/ Exclusion Criteria</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></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>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>12 Lead</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;2&lt;/sup&gt;</td>
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<td>X&lt;sup&gt;3&lt;/sup&gt;</td>
<td>X&lt;sup&gt;4&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Pregnancy test&lt;sup&gt;2&lt;/sup&gt; (local)</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Study Day</td>
<td>Screening</td>
<td>Randomization</td>
<td>Infusion 1</td>
<td>Infusions</td>
<td>Final IVUS</td>
<td>End of Treatment</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
<td>---------------</td>
<td>------------</td>
<td>-----------</td>
<td>------------</td>
<td>-----------------</td>
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<tr>
<td>-14 to 1</td>
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<td>(0-24 h)</td>
<td>10 ± 1</td>
<td>15 ± 1</td>
<td>22 ± 1</td>
<td>29 ± 1</td>
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<td></td>
<td></td>
<td></td>
<td>8 ± 1</td>
<td>36 ± 1</td>
<td>59 ± 2</td>
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</tr>
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</table>

Table 2: Schedule of Events for Subjects included in the AHA analysis

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Study Day</th>
<th>Infusion 1</th>
<th>Infusions</th>
<th>Final IVUS</th>
<th>End of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines</td>
<td></td>
<td>X</td>
<td>X X X X X X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Anti-MDCO-216 antibodies</td>
<td></td>
<td>X X X X X X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>PD parameters</td>
<td></td>
<td>X</td>
<td>X X X X X X</td>
<td>X X X X X</td>
<td></td>
</tr>
<tr>
<td>Coronary Angiogram</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>IVUS Examination</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X X X X X</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Study Drug Administration</td>
<td></td>
<td>X X X X X X</td>
<td>X X X X X</td>
<td>X X X X X</td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X X X X X</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>AE Reporting</td>
<td></td>
<td>X X X X X X</td>
<td>X X X X X</td>
<td>X X X X X</td>
<td></td>
</tr>
<tr>
<td>SAE Reporting</td>
<td></td>
<td>X X X X X X</td>
<td>X X X X X</td>
<td>X X X X X</td>
<td></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.

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.

7 Analysis collection is prior to the infusion start.

8 Urinary analysis collection is prior to the infusion start.

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

10 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.

11 PD samples – Collected prior to each infusion and then at 2 and 4 hours after start of infusion.

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

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

14 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.
2. OBJECTIVES AND STUDY DESIGN

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 and apolipoproteins.
3. ANALYSIS POPULATIONS

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

3.1 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.

3.2 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 evaluable assessment (in the eCRF data the fields RANDOM.IVUSQUAB and RANDOM.IVUSQUAF both as ‘acceptable’) are considered mITT. Treatment classification will be based on the randomized treatment. This will be the primary population for analysis of the primary and secondary endpoints.

3.3 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.
4. ANALYSIS ENDPOINTS

4.1. PRIMARY ENDPOINT

The primary endpoint of this analysis 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:

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

where \( PAV \) is calculated as:

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

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

4.2. SECONDARY ENDPOINTS

The secondary endpoints of this analysis 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:

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

  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:

  \[ \text{TAV (Day 36) - TAV (baseline)} \]
• Change in TAV for the 10 mm subsegment with the greatest disease burden at baseline

\[ \text{TAV}_{10 \text{ mm} \ (\text{D36})} - \text{TAV}_{10 \text{ mm} \ (\text{baseline})} \]

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:

\[ \sum (\text{EEMCSA} - \text{LUMENCSA}) \]

• 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.

4.3. SAFETY ENDPOINTS

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

5.1. 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).

Unless otherwise specified for repeat pre-baseline assessments, the results from the last assessment made before or at the start of study medication will be used as baseline for treated subjects. The last assessment value on or before randomization will be considered as baseline for those who are randomized but not treated.

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

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

5.2 Subject Disposition and Study Completion

The number of subjects included in each study population (i.e., ITT, mITT, and safety) will be presented. The number and percentage of subjects who completed and discontinued will be summarized.

5.3 Demographics and Baseline Characteristics

Demographics including age (years), sex, race/ethnicity, height, BMI, statin use, weight (kg), baseline characteristics including medical history, targeted cardiovascular medical history, vital signs, and baseline laboratory assessments will be summarized by descriptive statistics for all populations (ITT, mITT, and safety).

5.4 Prior and Concomitant Medication

Prior (pre-baseline) and concomitant medications (baseline or later) in addition to the study drug will be summarized descriptively using the ITT, mITT, and safety populations.

Separately, Summary of Baseline Lipid Modifying therapies will be tabulated by Class Name, Preferred Term, and Dose.
Prior and concomitant medications will be coded using the WHO Drug Dictionary, version Sept. 2014. Subjects will be counted only once within each period by medication.

5.5 Efficacy Analysis

Unless otherwise specified, all efficacy analyses will use the defined mITT as primary population.

5.7.1 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.

In addition, Above analysis for change in PAV will be performed for subject with statin prior to consent and for subjects without statin prior to consent (4 groups). Change in PAV will also be compared for site 148001 versus all other sites.

Waterfall plot will be provided for individual patient for change in PAV.(Two treatment groups represented by two colors). Waterfall plot for individual patient with and without statin prior to consent will also be provided for PAV(Four groups represented by four different colors).

5.7.2 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 analysis for change in TAV will also be performed for subject with stain prior to consent and for subjects without statin prior to consent(4 groups).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. Additionally, the proportion of subject with atheroma regression will also be compared by with/without statin use prior consent and treatment(4 groups).
Waterfall plot will be provided for individual patient for change in TAV. (Two treatment groups represented by two colors). Waterfall plot for individual patient with and without statin prior to consent will also be provided for TAV (Four groups represented by four different colors). 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.

5.8 Safety Analyses

Overall safety is determined by treatment emergent adverse events (AEs), clinical laboratory abnormalities, and vital signs.

Unless otherwise specified, all safety analyses will use the defined safety population.

5.8.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 18.1 will be used for coding adverse events (AEs). An AE (classified as preferred term) occurring during the study will be counted as a TEAE if:

- It is not present at baseline, or
- If it is present at baseline but increased in severity after the initiation of study medication.

If more than one AE with the same preferred term was reported pre-baseline, then the report with the greatest intensity is used as the benchmark for comparison to post-baseline reports of events with that preferred term.

Summaries of the number and percent of subjects with at least one SAE or TEAE and the number and percent of subjects with at least one severe AE, classified by preferred term and system organ class, will be provided. Comparisons of the proportion of subjects who experience treatment-related AEs will be made between treatment groups. 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 (as indicated by the investigators), respectively.

Any AEs with missing relationship with study drug will be considered as related AE.

Critical Labs (CK, ALT, AST, BILI) will be summarized by treatment group.

5.8.5 Laboratory Assessments

Clinical laboratory assessments for safety include hematology, clinical chemistry, coagulation, urinalysis, cytokines and anti-MDCO-216 antibodies. Absolute changes and percent changes from baseline in laboratory test values will be summarized by treatment
group at each time point. If applicable, analyses will also be performed by treatment
group for number and percent of subjects with predefined laboratory values considered
clinically significant.

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 will 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 drug infusion. Details are provided in the
schedule of assessments.

5.9 Assessment of Pharmacodynamics
Pharmacodynamics collected at scheduled timepoints will be summarized by descriptive
statistics comprising N, mean (SD), median, quartiles (Q1, Q3), minimum, and
maximum. Graphic display may also be presented.
The effects of MDCO-216 on PD parameters and biomarkers which may include but not
limited to cholesterol efflux, characterization of lipoprotein particles, determination of
total and free cholesterol in different lipoprotein subsets.

5.9.1 Lipid Profile
Assays for lipid profile assessments will be conducted at a central laboratory. The
parameters to be analyzed are the following:

- Total Cholesterol
- Triglyceride
- HDL - Cholesterol (ppt)
- LDL - Cholesterol (ppt calc)
- LDL-C (Ultracentrifugation)
- Apolipoprotein AI

5.10. 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 Atherosclerosis Imaging Core Laboratory (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.

Coronary angiography and IVUS will be performed at baseline as well as Day 36. Frequencies and percentage of the following at each visit will be presented by treatment group:

- Coronary angiogram done (yes/no)
- IVUS done (yes/no)
- Access site (femoral/radial/other)
- PCI performed prior to baseline IVUS (yes/no)
7. COMPUTER METHODS

Statistical analyses will be performed using SAS (version 9.2 or later version).
8. CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL

There are no changes to the analyses specified in the protocol.
REFERENCES

- MDCO-216 Phase 2a Pilot Study_Amend1.pdf
9. APPENDIX: List of AHA Late Breaking Clinical Trial Analysis

All analyses with two treatment group: MDCO-216 vs Placebo

**Baseline Data**

*(Tables)*

Baseline demographics
Baseline medical history including targeted CV history
Baseline con meds with lipid modifying therapies by dose
Baseline lipids

**IVUS (BL to Day 36)**

*(Tables)*

Percent Atheroma Volume (PAV)
Total Atheroma Volume (TAV)
Percent Atheroma Volume Most Diseased 10mm Segment
PAV with and without statin prior to consent (4 groups)
TAV with and without statin prior to consent (4 groups)
% Regressors (and regression less than baseline)
% Regressors with and without statin (4 groups)
PAV site 148001 versus all other sites

**Figures:**

Waterfall plots for individual patients for Change in PAV
Waterfall plots for individual patients for Change TAV
Waterfall plots for individual patients with and without statin for Change in PAV (4 groups)
Waterfall plots for individual patients with and without statin for Change TAV (4 groups)

**Lipids (BL to Day 36)**

*(Tables and figures)*

Total cholesterol
HDL-C
LDL-C
TG
Apo A1

**Safety (BL to Day 36)**

*(Tables)*

Treatment emergent AEs
Treatment emergent SAEs
Critical labs (CK, ALT, AST, BILI)

**Plus from second transfer all available data on date of data transfer (incomplete data set: % TBD)**

Lipids updated to include Day 59
SAEs updated to include Day 36 to Day 59
Critical labs (CK, ALT, AST, ALP, BILI) updated to include Day 36 to 59