Clinical trial results:
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.

Summary

EudraCT number	2015-000826-13
Trial protocol	CZ HU NL PL
Global end of trial date	26 October 2016

Results information

Result version number	v1 (current)
This version publication date	02 August 2017
First version publication date	02 August 2017

Trial information

Trial identification

Sponsor protocol code	MDCO-APO-15-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02678923
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Medicines Company
Sponsor organisation address	8 Sylvan Way, Parsippany, United States, 07054
Public contact	Global Health Science Center, The Medicines Company, 001 8889776326, medical.information@themedco.com
Scientific contact	Global Health Science Center, The Medicines Company, 001 8889776326, medical.information@themedco.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 October 2016
Global end of trial reached?	Yes
Global end of trial date	26 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was a proof-of-concept, placebo-controlled, double-blind, randomized trial in participants with a recent acute coronary syndrome (ACS) to evaluate the efficacy, pharmacokinetics, safety, tolerability, disease progression measures by intravascular ultrasound (IVUS), and pharmacodynamics of MDCO-216 infusion. Eligible participants were randomized to receive 5 infusions of MDCO-216 20 milligrams/kilogram (mg/kg) or placebo in a 1:1 ratio.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Poland: 83
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	Hungary: 14
Worldwide total number of subjects	126
EEA total number of subjects	119

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	78
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening procedures were performed up to 14 days prior to the first dose of study drug. All screening procedures were completed prior to randomization and the first dose of study drug.

Period 1

Period 1 title	MDCO-216 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Blinding implementation details:

The site pharmacist and/or qualified designee was the only team member at the site level who was unblinded to treatment assignment to allow for preparation of study drug. The study drug supply was not blinded. The Sponsor and Sponsor's designee involved in monitoring the pharmacy data were also unblinded. The infusion bag containing the study medication was identified with the participant's identification number, but did not identify the specific drug product.

Arms

Are arms mutually exclusive?	Yes
Arm title	MDCO-216

Arm description:

20 mg/kg of MDCO-216 administered intravenously (IV) as a 360 milliliters (mL) infusion over 2 hours on Days 1, 8, 15, 22, and 29.

Arm type	Experimental
Investigational medicinal product name	MDCO-216
Investigational medicinal product code	
Other name	Recombinant Apo A-I Milano (rApoA-IM)
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants randomized to the MDCO-216 group received MDCO-216 20 mg/kg infused IV over 2 hours in a 360 mL volume on Days 1, 8, 15, 22, and 29.

Arm title	Placebo

Arm description:

360 mL of placebo (0.9% sodium chloride [NaCl] solution) infusion, IV, over 2 hours on Days 1, 8, 15, 22, and 29.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	NaCl Solution
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants randomized to the placebo group received 360 mL normal saline (0.9% w/v sodium chloride) infused IV over 2 hours on Days 1, 8, 15, 22, and 29.

Number of subjects in period 1[1]	MDCO-216	Placebo
Started	58	64
Received 1 Dose of Study Drug	58	64
Completed	53	62
Not completed	5	2
Did Not Return for Study Visits	1	-
Consent withdrawn by subject	3	2
Lost to follow-up	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Four randomized participants had protocol deviations and were discontinued before receiving any study drug.

Baseline characteristics

Reporting groups	
Reporting group title	MDCO-216
Reporting group description:	
20 mg/kg of MDCO-216 administered intravenously (IV) as a 360 milliliters (mL) infusion over 2 hours on Days 1, 8, 15, 22, and 29.	
Reporting group title	Placebo
Reporting group description:	
360 mL of placebo (0.9% sodium chloride [NaCl] solution) infusion, IV, over 2 hours on Days 1, 8, 15, 22, and 29.	

Reporting group values	MDCO-216	Placebo	Total
Number of subjects	58	64	122
Age categorical			
Safety population included all participants who received at least one infusion of study drug.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	36	39	75
From 65-84 years	22	25	47
85 years and over	0	0	0
Gender categorical			
Safety population included all participants who received at least one infusion of study drug.			
Units: Subjects			
Female	13	16	29
Male	45	48	93
Region of Enrollment Units: Subjects			
Canada	3	3	6
Czech Republic	3	2	5
Hungary	6	8	14
Netherlands	8	8	16
Poland	38	43	81

End points

End points reporting groups

Reporting group title	MDCO-216
Reporting group description:	
20 mg/kg of MDCO-216 administered intravenously (IV) as a 360 milliliters (mL) infusion over 2 hours on Days 1, 8, 15, 22, and 29.	
Reporting group title	Placebo
Reporting group description:	
360 mL of placebo (0.9% sodium chloride [NaCl] solution) infusion, IV, over 2 hours on Days 1, 8, 15, 22, and 29.	
Subject analysis set title	MDCO-216
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Modified intent-to-treat (mITT) population included all participants who were screened, enrolled, randomized, received at least one infusion of study drug, and who had an evaluable Baseline and Follow-up IVUS assessment.	
Subject analysis set title	Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
mITT population included all participants who were screened, enrolled, randomized, received at least one infusion of study drug and who had an evaluable Baseline and Follow-up IVUS assessment.	

Primary: Change From Baseline In Percent Atheroma Volume (PAV) At Day 36

End point title	Change From Baseline In Percent Atheroma Volume (PAV) At Day 36
End point description:	
Change from Baseline to Day 36 post-randomization in PAV in a targeted (imaged) coronary artery for all anatomically comparable slices, as determined by IVUS. The change is calculated by subtracting the value at Baseline from the value at Day 36, with positive numbers to represent increases and negative numbers to represent decreases. Change in PAV was analyzed using an analysis of covariance (ANCOVA) model that included Baseline PAV as a covariate and treatment group as factor. Least Squares (LS) mean was adjusted for stratification factors of country and prior statin use.	
End point type	Primary
End point timeframe:	
Baseline, Day 36	

End point values	MDCO-216	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	61		
Units: change in percent				
least squares mean (standard error)	-0.21 (± 0.386)	-0.94 (± 0.382)		

Statistical analyses

Statistical analysis title	Change From Baseline In PAV At Day 36

Statistical analysis description:

Change in PAV was analyzed using an analysis of covariance (ANCOVA) model that included baseline PAV as a covariate and treatment group as factor. Least Squares (LS) mean was adjusted for stratification factors of country and prior statin use.

Comparison groups	MDCO-216 v Placebo
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0738 [1]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	1.52

Notes:

[1] - Baseline parameter value as a covariate and treatment group as factor, adjusting for country and prior statin use.

Secondary: Change From Baseline In Total Atheroma Volume (TAV) At Day 36

End point title	Change From Baseline In Total Atheroma Volume (TAV) At Day 36

End point description:

Change from Baseline to Day 36 post-randomization in normalized TAV in a targeted (imaged) coronary artery for all anatomically comparable slices, as determined by IVUS. The change is calculated by subtracting the value at Baseline from the value at Day 36, with positive numbers to represent increases and negative numbers to represent decreases. Change in TAV was analyzed using an analysis of covariance (ANCOVA) model that included Baseline TAV as a covariate and treatment group as factor. LS mean was adjusted for stratification factors of country and prior statin use.

End point type	Secondary

End point timeframe:

Baseline, Day 36

End point values	MDCO-216	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	61		
Units: cubic millimeter (mm^3)				
least squares mean (standard error)	-6.33 (± 3.425)	-7.89 (± 3.354)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In TAV For The 10 Millimeters (mm) Subsegment With The Greatest Disease Burden At Day 36

End point title	Change From Baseline In TAV For The 10 Millimeters (mm)

	Subsegment With The Greatest Disease Burden At Day 36

End point description:

Change in TAV from Baseline to Day 36 post-randomization of the most diseased 10-mm subsegment, as determined by IVUS. The change is calculated by subtracting the value at Baseline from the value at Day 36, with positive numbers to represent increases and negative numbers to represent decreases. Change in TAV was analyzed using an analysis of covariance (ANCOVA) model that included Baseline TAV for the most diseased 10-mm subsegment as a covariate and treatment group as factor. LS mean was adjusted for stratification factors of country and prior statin use.

End point type	Secondary

End point timeframe:

Baseline, Day 36

End point values	MDCO-216	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	61		
Units: mm^3				
least squares mean (standard error)	-2.16 (± 1.809)	-1.74 (± 1.908)		

Statistical analyses

No statistical analyses for this end point

Secondary: Participants With Regression Of Coronary Atherosclerosis As Measured By A PAV Change Greater Than 2 Standard Deviations Of Test-Retest Measurement Variability

End point title	Participants With Regression Of Coronary Atherosclerosis As Measured By A PAV Change Greater Than 2 Standard Deviations Of Test-Retest Measurement Variability

End point description:

The number of participants with regression of coronary atherosclerosis is presented. For this Outcome Measure, the regression of coronary atherosclerosis is defined as a reduction in PAV from Baseline to Day 36 of greater than 2 standard deviations of the test-retest variability.

End point type	Secondary

End point timeframe:

Baseline through Day 36

End point values	MDCO-216	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[2]	0[3]		
Units: Participants				

Notes:

[2] - Test-retest requires IVUS to be done twice at the same time point and retest IVUS was not done.

[3] - Test-retest requires IVUS to be done twice at the same time point and retest IVUS was not done.

Statistical analyses

No statistical analyses for this end point

Secondary: Participants With Regression Of Coronary Atherosclerosis As Measured By A PAV Change <0

End point title	Participants With Regression Of Coronary Atherosclerosis As Measured By A PAV Change <0

End point description:

The number of participants with regression of coronary atherosclerosis is presented. For this Outcome Measure, the regression of coronary atherosclerosis is defined as a change in PAV from Baseline to Day 36 of less than zero.

End point type	Secondary

End point timeframe:

Baseline through Day 36

End point values	MDCO-216	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	61		
Units: participants	29	41		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 59 days (±2 days) post randomization	
Adverse event reporting additional description:	
Safety population included all participants who received at least one infusion of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	MDCO-216
Reporting group description:	
20 mg/kg administered IV as a 360 mL infusion over 2 hours on Days 1, 8, 15, 22, and 29.	
Reporting group title	Placebo
Reporting group description:	
360 mL (0.9% NaCl solution) infusion, IV, over 2 hours on Days 1, 8, 15, 22, and 29.	

Serious adverse events	MDCO-216	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 58 (17.24%)	7 / 64 (10.94%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Echocardiogram abnormal			
subjects affected / exposed	1 / 58 (1.72%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Coronary artery restenosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 58 (1.72%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 58 (1.72%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 58 (1.72%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	3 / 58 (5.17%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystole			
subjects affected / exposed	1 / 58 (1.72%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 58 (1.72%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vessel puncture site haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	0 / 58 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 58 (1.72%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	0 / 58 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	MDCO-216	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 58 (41.38%)	12 / 64 (18.75%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 58 (3.45%)	2 / 64 (3.13%)	
occurrences (all)	2	2	
Blood creatine phosphokinase			
subjects affected / exposed	0 / 58 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	

Vascular disorders Hypertension subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	2 / 64 (3.13%) 2	
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	1 / 64 (1.56%) 1	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4 4 / 58 (6.90%) 5	1 / 64 (1.56%) 1 1 / 64 (1.56%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	4 / 64 (6.25%) 4	
General disorders and administration site conditions Vessel puncture site haematoma subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	0 / 64 (0.00%) 0	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	0 / 64 (0.00%) 0	
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4	2 / 64 (3.13%) 4	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	0 / 64 (0.00%) 0	
Metabolism and nutrition disorders Gout			

subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	0 / 64 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported