Clinical trial results:
A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Tolerability and Efficacy of Intravenous Bendavia™ (MTP-131) on Reperfusion Injury in Patients Treated with Standard Therapy Including Primary PCI and Stenting for ST-segment Elevation Myocardial Infarction

Summary

EudraCT number	2011-002824-42
Trial protocol	HU
Global end of trial date	10 February 2015

Results information

Result version number	v1 (current)
This version publication date	02 August 2020
First version publication date	02 August 2020
Summary attachment (see zip file)	SPIRI-201 summary (SPIRI-201 summary.docx)

Trial information

Trial identification

Sponsor protocol code	SPIRI-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01572909
WHO universal trial number (UTN)	-
Other trial identifiers	IND : 105942

Notes:

Sponsors

Sponsor organisation name	Stealth BioTherapeutics Inc.
Sponsor organisation address	275 Grove Street, Suite 3-107, Newton, United States, MA 02466
Public contact	Jim Carr, Pharm.D. Chief Clinical Development Officer, Stealth BioTherapeutics Inc., 001 6176006888 , jim.carr@stealthbt.com
Scientific contact	Jim Carr, Pharm.D. Chief Clinical Development Officer, Stealth BioTherapeutics Inc., 001 6176006888 , jim.carr@stealthbt.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	23 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 November 2014
Global end of trial reached?	Yes
Global end of trial date	10 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate the impact of Bendavia on limiting the size of infarcted myocardium in patients with first time anterior wall ST-segment elevation myocardial infarction (STEMI) who have undergone successful reperfusion using primary percutaneous coronary intervention (PCI) and stenting.

Protection of trial subjects:

Written approval of the protocol, the final informed consent document, relevant supporting material and patient recruitment information were obtained from the independent ethics committee (IEC)/institutional review board (IRB) prior to study initiation.
The study was conducted in accordance with current applicable regulations, ICH guidelines and local legal requirements. Conduct of the trial complied with the principles that have their origins in the Declaration of Helsinki with emphasis on informed consent and maximizing participant safety.

Background therapy:

Standard-of-care therapy for reduction of reperfusion injury

Evidence for comparator: -

Actual start date of recruitment	21 June 2012
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	Poland: 143
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Hungary: 115
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	300
EEA total number of subjects	296

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	200
From 65 to 84 years	98
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Adult male and female subjects between the ages of 18 and 85 were recruited at 24 study centers in the United States, Poland, Germany, and Hungary.

Pre-assignment

Screening details:

Main inclusion criteria: adult males or females aged 18 years or older and less than 85 years old who had undergone PCI plus stenting with the time from onset of symptoms of cardiac ischemia to the time of initial PCI balloon inflation not exceeding 4 hours.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Active

Arm description:

Participants received Bendavia (MTP-131) as an IV infusion at 0.05 mg/kg/hr at least 15 minutes but no more than 1 hour prior to the anticipated reperfusion event and continued through approximately 1 hour following re-establishment of blood flow through the culprit vessel via primary percutaneous coronary intervention and stenting.

Arm type	Active comparator
Investigational medicinal product name	Bendavia™
Investigational medicinal product code	
Other name	MTP-131, Elamipretide
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bendavia™ was administered intravenously at 0.05 mg/kg/hr at least 15, but no more than 60 minutes, prior to the anticipated time of the PCI, and continued for 1 hour after re-establishment of blood flow through the culprit vessel.

Arm title	Placebo

Arm description:

Participants received placebo as an IV infusion at 60 mL/hr at least 15 minutes but no more than 1 hour prior to the anticipated reperfusion event and continued through approximately 1 hour following re-establishment of blood flow through the culprit vessel via primary percutaneous coronary intervention and stenting.

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

Dosage and administration details:

Participants received placebo as an IV infusion at 60 mL/hr at least 15 minutes but no more than 1 hour prior to the anticipated reperfusion event and continued through approximately 1 hour following re-establishment of blood flow through the culprit vessel via primary percutaneous coronary intervention and stenting.

Number of subjects in period 1[1]	Active	Placebo
Started	150	147
Completed	118	122
Not completed	32	25
Infarct, comorbidity, Pt refusal of exam	-	3
Consent withdrawn by subject	12	11
Physician decision	1	1
Adverse event, non-fatal	7	2
Death	3	1
Lost to follow-up	8	7
Technical issues	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: Three patients lost between screening and baseline.

Baseline characteristics

Reporting groups	
Reporting group title	Active
Reporting group description:	
Participants received Bendavia (MTP-131) as an IV infusion at 0.05 mg/kg/hr at least 15 minutes but no more than 1 hour prior to the anticipated reperfusion event and continued through approximately 1 hour following re-establishment of blood flow through the culprit vessel via primary percutaneous coronary intervention and stenting.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo as an IV infusion at 60 mL/hr at least 15 minutes but no more than 1 hour prior to the anticipated reperfusion event and continued through approximately 1 hour following re-establishment of blood flow through the culprit vessel via primary percutaneous coronary intervention and stenting.	

Reporting group values	Active	Placebo	Total
Number of subjects	150	147	297
Age categorical			
Age category			
Units: Subjects			
Adults (18-64 years)	96	101	197
From 65-84 years	53	45	98
85 years and over	1	1	2
Gender categorical			
Units: Subjects			
Female	45	28	73
Male	105	119	224

End points

End points reporting groups

Reporting group title	Active

Reporting group description:

Participants received Bendavia (MTP-131) as an IV infusion at 0.05 mg/kg/hr at least 15 minutes but no more than 1 hour prior to the anticipated reperfusion event and continued through approximately 1 hour following re-establishment of blood flow through the culprit vessel via primary percutaneous coronary intervention and stenting.

Reporting group title	Placebo

Reporting group description:

Participants received placebo as an IV infusion at 60 mL/hr at least 15 minutes but no more than 1 hour prior to the anticipated reperfusion event and continued through approximately 1 hour following re-establishment of blood flow through the culprit vessel via primary percutaneous coronary intervention and stenting.

Primary: Area Under the Curve (AUC) of Serum Creatine Kinase Isoenzyme Type Muscle-brain (CK-MB)

End point title	Area Under the Curve (AUC) of Serum Creatine Kinase Isoenzyme Type Muscle-brain (CK-MB)

End point description:

Infarct size as measured by the AUC of serum CK-MB at 24 and 72 hours post-PCI

End point type	Primary

End point timeframe:

The initial 24 and 72 hours post-percutaneous coronary intervention (PCI)

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	60		
Units: ng*hr/mL				
arithmetic mean (standard deviation)				
72 Hours	6582.0 (± 3270.6)	6738.3 (± 3775.4)		
24 Hours	5252.2 (± 2667.9)	5471.9 (± 3270.7)		

Statistical analyses

Statistical analysis title	Statistical methods

Statistical analysis description:

Continuous variables were analyzed using analysis of covariance (ANCOVA) or a one-way analysis of variance (ANOVA).
Unless otherwise indicated, continuous variables (eg, age, volume of myocardial infarction) were summarized by treatment group using descriptive statistics consisting of number of patients, mean, median, standard deviation or standard error (as appropriate), minimum, and maximum values.

Comparison groups	Active v Placebo

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)

Secondary: Ratio of Volume of Infarcted Myocardium to Left Ventricular Mass

End point title	Ratio of Volume of Infarcted Myocardium to Left Ventricular Mass

End point description:

Cardiac infarct size calculated as the ratio of volume of infarcted myocardium to left ventricular mass at Day 30 as
measured by MRI.

End point type	Secondary

End point timeframe:

Day 30 + 7

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	47		
Units: ratio				
arithmetic mean (standard deviation)	242.3 (± 87.3)	225.2 (± 90.70)		

Statistical analyses

No statistical analyses for this end point

Secondary: Thrombosis in Myocardial Infarction (TIMI) Perfusion Grade Flow at Completion of PCI

End point title	Thrombosis in Myocardial Infarction (TIMI) Perfusion Grade Flow at Completion of PCI

End point description:

TIMI perfusion grade flow at completion of PCI will be categorized as 0,1, or 1.5, 2 or 2.5, 3, and treated as ordinal data,
where higher score means better perfusion and lower score means worse perfusion and worse outcome.

End point type	Secondary

End point timeframe:

Initiation to Completion of PCI, no longer than 4 hours

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: participants				
Flow Grade 0	0	0		
Flow Grade 1 or 1.5	0	0		
Flow Grade 2 or 2.5	6	7		
Flow Grade 3	52	53		

Statistical analyses

No statistical analyses for this end point

Secondary: Corrected TIMI Frame Count

End point title	Corrected TIMI Frame Count

End point description:

Corrected TIMI Frame Count at Completion of PCI as captured by angiogram and analyzed as a continuous variable.

End point type	Secondary

End point timeframe:

Completion of PCI, no longer than 4 hours

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: corrected frame count				
arithmetic mean (standard deviation)	79.7 (± 122.8)	166.0 (± 286.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: ST-Segmented Elevation From Pre-PCI to 24 Hours Post-PCI and Presence of ST-Segmented Resolution

End point title	ST-Segmented Elevation From Pre-PCI to 24 Hours Post-PCI and Presence of ST-Segmented Resolution

End point description:

ST-Segmented Elevation from pre-PCI to 24 hours post-PCI and Presence of ST-Segmented Resolution by ECG

End point type	Secondary

End point timeframe:

pre-PCI to 24 hours post-PCI

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	57		
Units: participants				
Complete (>=70% resolution)	30	29		
Partial (<70% resolution)	22	21		
None (<30% resolution)	4	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Serum Creatinine From Baseline

End point title	Change in Serum Creatinine From Baseline

End point description:

Change in serum creatinine, from baseline (prior to study drug administration) to Day 30 +7 post-PCI

End point type	Secondary

End point timeframe:

Day 30 +7

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: umol/L				
arithmetic mean (standard deviation)	10.55 (± 17.642)	88.04 (± 22.462)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Estimated Glomerular Filtration Rate (eGFR) From Baseline

End point title	Change in Estimated Glomerular Filtration Rate (eGFR) From Baseline

End point description:

Change in eGFR from baseline (prior to study drug administration) to Day 30 +7 post-PCI

End point type	Secondary

End point timeframe:

Day 30 +/- 7

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	50		
Units: mL/min/SSA				
arithmetic mean (standard deviation)	-12.33 (± 18.873)	-8.94 (± 14.242)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cystatin C Change From Baseline

End point title	Cystatin C Change From Baseline

End point description:

Change in Cystatin C from baseline (prior to study drug administration) to Day 30 +7 post-PCI

End point type	Secondary

End point timeframe:

Day 30 + 7

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	49		
Units: mg/L				
arithmetic mean (standard deviation)	0.19 (± 0.341)	0.19 (± 0.226)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUC of Troponin 1 Enzyme

End point title	AUC of Troponin 1 Enzyme

End point description:

Infarct size as calculated by the AUC of Troponin I Enzyme over the initial 24 and 72 hours post-PCI

End point type	Secondary

End point timeframe:

Initial 24 and 72 hours post-PCI

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	60		
Units: ng*hr/mL				
arithmetic mean (standard deviation)				
72 Hours	5422.9 (± 3430.9)	4647.2 (± 2834.7)		
24 Hours	3301.4 (± 2192.9)	2850.4 (± 1640.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Blood Urea Nitrogen (BUN) Change From Baseline

End point title	Blood Urea Nitrogen (BUN) Change From Baseline

End point description:

Blood Urea Nitrogen (BUN) Change from baseline (prior to study drug administration) to Day 30 + 7 post-PCI

End point type	Secondary

End point timeframe:

Baseline to Day 30

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	51		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.13 (± 1.603)	0.13 (± 2.207)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number and Percent of Grade 1 Episode of Contrast-Induced Nephropathy Post-PCI

End point title	Number and Percent of Grade 1 Episode of Contrast-Induced Nephropathy Post-PCI

End point description:

Number of Participants with Grade 1 Episode of Contrast-Induced Nephropathy within 48 hours of initial PCI or MRI,
based on lab data.

End point type	Secondary

End point timeframe:

Baseline to 48 hours post PCI or MRI

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: participants				
Yes	17	11		
No	41	49		

Statistical analyses

No statistical analyses for this end point

Secondary: Immediate Myocardial Complications: Ventricular Tachycardia or Fibrillation

End point title	Immediate Myocardial Complications: Ventricular Tachycardia or Fibrillation

End point description:

Number and percent of participants with Immediate Myocardial Complications: Ventricular Tachycardia or Fibrillation
Requiring Medical Intervention

End point type	Secondary

End point timeframe:

Baseline up to 1 hour post-PCI

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: participants				
Yes	2	3		
No	56	57		

Statistical analyses

No statistical analyses for this end point

Secondary: Immediate Myocardial Complications: Mechanical Complications

End point title	Immediate Myocardial Complications: Mechanical Complications

End point description:

Number and Percent of Participants with Immediate Myocardial Complications: Mechanical Complications: (Free wall
Rupture, Ventricular Septal Defect, Ischemic Mitral Regurgitation)

End point type	Secondary

End point timeframe:

Baseline up to 1 hour post-PCI

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: Participants	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Emergency Use of Medications During PCI Procedure

End point title	Emergency Use of Medications During PCI Procedure

End point description:

Emergency Use of Nitroprusside, Calcium Channel Blocker, Adenosine Administration During the PCI Procedure

End point type	Secondary

End point timeframe:

Initiation to Completion of PCI, no longer than 4 hours

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: Participants				
Yes	5	3		
No	53	57		

Statistical analyses

No statistical analyses for this end point

Secondary: ProB-type Natriuretic Peptide (NT-proBNP) Change From Baseline to Day 30

End point title	ProB-type Natriuretic Peptide (NT-proBNP) Change From Baseline to Day 30

End point description:

NT-proBNP: Change from baseline to Day 30 +7 (Laboratory marker for chronic heart failure (CHF) and systemic

inflammation.)

End point type	Secondary
End point timeframe: Baseline to Day 30	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	51		
Units: pg/mL				
arithmetic mean (standard deviation)	1828.45 (± 3427.408)	1582.67 (± 1502.985)		

Statistical analyses

No statistical analyses for this end point

Secondary: High Sensitivity C-Reactive Protein (hsCRP): Change From Baseline to Day 30

End point title	High Sensitivity C-Reactive Protein (hsCRP): Change From Baseline to Day 30
End point description: High Sensitivity C-Reactive Protein (hsCRP): Change from baseline to Day 30 +7 (Laboratory Marker for CHF and Systemic Inflammation)	
End point type	Secondary
End point timeframe: Baseline to Day 30	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	45		
Units: mg/L				
arithmetic mean (standard deviation)	-1.03 (± 7.072)	-0.91 (± 7.024)		

Statistical analyses

No statistical analyses for this end point

Secondary: Left Ventricular (LV) Ejection Fraction (%)

End point title	Left Ventricular (LV) Ejection Fraction (%)

End point description:

Difference in Left Ventricular (LV) Ejection Fraction (%) from Day 4 To Day 30

End point type	Secondary

End point timeframe:

Day 4 to Day 30

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	53		
Units: percentage of blood volume				
arithmetic mean (standard deviation)	2.1 (± 6.4)	2.5 (± 8.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Difference Between Left Ventricular End Diastolic Volume, Corrected

End point title	Difference Between Left Ventricular End Diastolic Volume, Corrected

End point description:

Difference between Left Ventricular End Diastolic Volume Corrected for Body Surface Area between Day 4 and Day 30

End point type	Secondary

End point timeframe:

Day 4 and Day 30

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	52		
Units: mL/m2				
arithmetic mean (standard deviation)	8.6 (± 12.6)	6.2 (± 15.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Difference Between Left Ventricular End Systolic Volume, Corrected

End point title	Difference Between Left Ventricular End Systolic Volume, Corrected

End point description:

Difference between Left Ventricular End Systolic Volume Corrected for Body Surface Area from Day 4 and Day 30

End point type	Secondary

End point timeframe:

Day 4 and Day 30

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	52		
Units: mL/m²				
arithmetic mean (standard deviation)	2.7 (± 8.0)	1.5 (± 12.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Chronic Heart Failure

End point title	Chronic Heart Failure

End point description:

Number and Percentage of Patients with Clinical Events: Chronic Heart Failure beginning within 24 hours after PCI but
within the duration of the index hospitalization (Subjects with CHF started within 24 hours after the last balloon deflation
while the patient was still in the hospital {including patients who had missing discharge date}).

End point type	Secondary

End point timeframe:

Within 24 hours after PCI

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: Participants				
Yes	8	15		
No	50	45		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 21 June 2012 to 22 September 2014	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups	
Reporting group title	Active
Reporting group description: Participants received Bendavia (MTP-131) as an IV infusion at 0.05 mg/kg/hr at least 15 minutes but no more than 1 hour prior to the anticipated reperfusion event and continued through approximately 1 hour following re-establishment of blood flow through the culprit vessel via primary percutaneous coronary intervention and stenting.	
Reporting group title	Placebo
Reporting group description: Participants received placebo as an IV infusion at 60 mL/hr at least 15 minutes but no more than 1 hour prior to the anticipated reperfusion event and continued through approximately 1 hour following re-establishment of blood flow through the culprit vessel via primary percutaneous coronary intervention and stenting.	

Serious adverse events	Active	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 150 (13.33%)	14 / 147 (9.52%)	
number of deaths (all causes)	3	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic Neoplasm			
subjects affected / exposed	0 / 150 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Rib Fracture			
subjects affected / exposed	1 / 150 (0.67%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternum Fracture			

subjects affected / exposed	1 / 150 (0.67%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Procedural Complication			
subjects affected / exposed	1 / 150 (0.67%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Pseudoaneurysm			
subjects affected / exposed	1 / 150 (0.67%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Femoral Artery Embolism			
subjects affected / exposed	1 / 150 (0.67%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	1 / 150 (0.67%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
subjects affected / exposed	0 / 150 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block			
subjects affected / exposed	0 / 150 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	0 / 150 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			

subjects affected / exposed	0 / 150 (0.00%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac Tamponade			
subjects affected / exposed	0 / 150 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic Shock			
subjects affected / exposed	4 / 150 (2.67%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary Artery Occlusion			
subjects affected / exposed	1 / 150 (0.67%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Stenosis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac Thrombus			
subjects affected / exposed	1 / 150 (0.67%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischemic Cardiomyopathy			
subjects affected / exposed	0 / 150 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	1 / 150 (0.67%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Fibrillation			

subjects affected / exposed	1 / 150 (0.67%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 150 (0.67%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 150 (0.67%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 147 (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			
Sudden cardiac death			
subjects affected / exposed	1 / 150 (0.67%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombosis in device			
subjects affected / exposed	2 / 150 (1.33%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 150 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			

subjects affected / exposed	0 / 150 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	0 / 150 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 150 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 150 (0.67%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 150 (1.33%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Infection			
subjects affected / exposed	1 / 150 (0.67%)	0 / 147 (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: 2 %

Non-serious adverse events	Active	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	133 / 150 (88.67%)	107 / 147 (72.79%)	
Vascular disorders			
Haematoma			

subjects affected / exposed	4 / 150 (2.67%)	4 / 147 (2.72%)	
occurrences (all)	4	4	
Hypertension			
subjects affected / exposed	11 / 150 (7.33%)	9 / 147 (6.12%)	
occurrences (all)	11	9	
Hypotension			
subjects affected / exposed	5 / 150 (3.33%)	5 / 147 (3.40%)	
occurrences (all)	5	5	
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	3 / 150 (2.00%)	1 / 147 (0.68%)	
occurrences (all)	3	1	
Non-cardiac chest pain			
subjects affected / exposed	9 / 150 (6.00%)	5 / 147 (3.40%)	
occurrences (all)	9	5	
Pyrexia			
subjects affected / exposed	5 / 150 (3.33%)	9 / 147 (6.12%)	
occurrences (all)	5	9	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 150 (4.00%)	3 / 147 (2.04%)	
occurrences (all)	6	3	
Dyspnoea			
subjects affected / exposed	2 / 150 (1.33%)	5 / 147 (3.40%)	
occurrences (all)	2	5	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 150 (6.00%)	14 / 147 (9.52%)	
occurrences (all)	9	14	
Claustrophobia			
subjects affected / exposed	1 / 150 (0.67%)	3 / 147 (2.04%)	
occurrences (all)	1	3	
Insomnia			
subjects affected / exposed	7 / 150 (4.67%)	1 / 147 (0.68%)	
occurrences (all)	7	1	
Investigations			

Blood potassium decreased			
subjects affected / exposed	2 / 150 (1.33%)	3 / 147 (2.04%)	
occurrences (all)	2	3	
Ejection fraction decreased			
subjects affected / exposed	4 / 150 (2.67%)	1 / 147 (0.68%)	
occurrences (all)	4	1	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	11 / 150 (7.33%)	6 / 147 (4.08%)	
occurrences (all)	11	6	
Atrial fibrillation			
subjects affected / exposed	6 / 150 (4.00%)	8 / 147 (5.44%)	
occurrences (all)	6	8	
Bradycardia			
subjects affected / exposed	0 / 150 (0.00%)	3 / 147 (2.04%)	
occurrences (all)	0	3	
Cardiac Failure			
subjects affected / exposed	28 / 150 (18.67%)	29 / 147 (19.73%)	
occurrences (all)	28	29	
Cardiac Failure Congestive			
subjects affected / exposed	5 / 150 (3.33%)	5 / 147 (3.40%)	
occurrences (all)	5	5	
Coronary Artery Disease			
subjects affected / exposed	5 / 150 (3.33%)	5 / 147 (3.40%)	
occurrences (all)	5	5	
Coronary artery stenosis			
subjects affected / exposed	3 / 150 (2.00%)	4 / 147 (2.72%)	
occurrences (all)	3	4	
Intracardiac thrombus			
subjects affected / exposed	9 / 150 (6.00%)	10 / 147 (6.80%)	
occurrences (all)	9	10	
Mitral Valve Incompetence			
subjects affected / exposed	3 / 150 (2.00%)	1 / 147 (0.68%)	
occurrences (all)	3	1	
Pericardial effusion			

subjects affected / exposed	0 / 150 (0.00%)	3 / 147 (2.04%)	
occurrences (all)	0	3	
Ventricular Tachycardia			
subjects affected / exposed	4 / 150 (2.67%)	4 / 147 (2.72%)	
occurrences (all)	4	4	
Ventricular extrasystoles			
subjects affected / exposed	4 / 150 (2.67%)	1 / 147 (0.68%)	
occurrences (all)	4	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 150 (2.00%)	2 / 147 (1.36%)	
occurrences (all)	3	2	
Headache			
subjects affected / exposed	6 / 150 (4.00%)	2 / 147 (1.36%)	
occurrences (all)	6	2	
Hypotonia			
subjects affected / exposed	3 / 150 (2.00%)	3 / 147 (2.04%)	
occurrences (all)	3	3	
Syncope			
subjects affected / exposed	3 / 150 (2.00%)	0 / 147 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 150 (4.00%)	6 / 147 (4.08%)	
occurrences (all)	6	6	
Thrombocytopenia			
subjects affected / exposed	3 / 150 (2.00%)	0 / 147 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 150 (0.67%)	4 / 147 (2.72%)	
occurrences (all)	1	4	
Diarrhoea			
subjects affected / exposed	4 / 150 (2.67%)	7 / 147 (4.76%)	
occurrences (all)	4	7	
Nausea			

subjects affected / exposed	9 / 150 (6.00%)	7 / 147 (4.76%)	
occurrences (all)	9	7	
Vomiting			
subjects affected / exposed	8 / 150 (5.33%)	7 / 147 (4.76%)	
occurrences (all)	8	7	
Renal and urinary disorders			
Renal Failure Chronic			
subjects affected / exposed	1 / 150 (0.67%)	3 / 147 (2.04%)	
occurrences (all)	1	3	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 150 (3.33%)	7 / 147 (4.76%)	
occurrences (all)	5	7	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 150 (2.00%)	4 / 147 (2.72%)	
occurrences (all)	3	4	
Urinary tract infection			
subjects affected / exposed	2 / 150 (1.33%)	3 / 147 (2.04%)	
occurrences (all)	2	3	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	12 / 150 (8.00%)	7 / 147 (4.76%)	
occurrences (all)	12	7	
Glucose Tolerance Impairment			
subjects affected / exposed	5 / 150 (3.33%)	6 / 147 (4.08%)	
occurrences (all)	5	6	
Hypercholesterolaemia			
subjects affected / exposed	30 / 150 (20.00%)	19 / 147 (12.93%)	
occurrences (all)	30	19	
Hyperlipidaemia			
subjects affected / exposed	6 / 150 (4.00%)	9 / 147 (6.12%)	
occurrences (all)	6	9	
Hypokalaemia			
subjects affected / exposed	27 / 150 (18.00%)	27 / 147 (18.37%)	
occurrences (all)	27	27	

Hyponatraemia			
subjects affected / exposed	3 / 150 (2.00%)	2 / 147 (1.36%)	
occurrences (all)	3	2	
Type 2 diabetes mellitus			
subjects affected / exposed	3 / 150 (2.00%)	1 / 147 (0.68%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2012	• Inclusion criteria for menopause was clarified as >12 months of no menses. • Maximal infusion time for investigational product was adjusted to <4 hours. • Primary Analysis Population must have received ≥10 minutes pre- and ≥45 minutes post-PCI infusion of study drug. • Added STAT local serum sodium and serum creatinine, drawn prior to the PCI and if the sodium was <135 mEq/L or the eGFR was <50 mL/min, the study drug infusion was stopped and repeat values obtained.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported