Clinical trial results:
Bivalirudin Infusion for Ventricular Infarction Limitation (BIVAL)

Summary

EudraCT number	2012-002314-39
Trial protocol	NL IT
Global end of trial date	14 June 2016

Results information

Result version number	v1 (current)
This version publication date	08 June 2017
First version publication date	08 June 2017

Trial information

Trial identification

Sponsor protocol code	MDCO-BIV-12-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02565147
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Medicines Company (Schweiz) GmbH
Sponsor organisation address	Talstrasse 59, Zurich, Switzerland, 8001
Public contact	Global Health Science Center, The Medicines Company, 41 044 828 1084, medical.information@themedco.com
Scientific contact	Global Health Science Center, The Medicines Company, 41 044 828 1084, 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	17 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 June 2016
Global end of trial reached?	Yes
Global end of trial date	14 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine whether treatment with bivalirudin, compared with treatment with heparin (unfractionated heparin [UFH]), for primary percutaneous coronary intervention (PPCI) in large ST-segment elevation myocardial infarction (STEMI) can reduce infarct size assessed by cardiac magnetic resonance (CMR) 5 days (defined as 5 days ±72 hours [h] from randomisation) after PPCI.
Results for all participants enrolled into this trial (BIVAL) are presented.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) 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	09 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 43
Country: Number of subjects enrolled	France: 35
Worldwide total number of subjects	78
EEA total number of subjects	78

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)	48

From 65 to 84 years	26
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening occurred minutes prior to randomisation and included review of inclusion/exclusion criteria, signed informed consent, aspirin and P2Y12 administration when feasible, 12-lead electrocardiogram, clinical laboratory assessments, PPCI eligibility confirmation, flow assessment, and angiographic assessment for a large myocardial infarction.

Period 1

Period 1 title	BIVAL (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

The primary endpoint was evaluated by a core lab totally blinded to clinical information and the treatment groups.

Arms

Are arms mutually exclusive?	Yes
Arm title	PPCI with Bivalirudin

Arm description:

Bivalirudin was administered as a bolus (0.75 milligram [mg]/kilogram [kg]) and an infusion (1.75 mg/kg/h) for the duration of the PPCI and continued for the first 4 h after completion of the procedure.

Arm type	Experimental
Investigational medicinal product name	Bivalirudin
Investigational medicinal product code	
Other name	Angiomax, Angiox
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous bolus use , Intravenous use

Dosage and administration details:

All participants randomised to the bivalirudin group received a bivalirudin bolus of 0.75 mg/kg and an infusion of 1.75 mg/kg/h for the duration of the procedure and the 4 h after the procedure.

Arm title	PPCI with Heparin

Arm description:

UFH administered as a bolus according to standard of care for completion of PPCI per site. An activated clotting time (ACT) ≥250 seconds (s) at the end of the procedure was recommended.

Arm type	Active comparator
Investigational medicinal product name	Unfractionated Heparin
Investigational medicinal product code	
Other name	Heparin
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

All participants randomised to the UFH group received a UFH bolus according to the standard of care for completion of PPCI per site. An ACT ≥250 s at the end of the procedure was recommended.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Despite the obvious benefits of a double-blind design, the logistics of a double-blind approach are exceedingly difficult in the emergent setting of PPCI. The open-label design did not add any logistical hurdles and therefore allowed for timely reperfusion in these STEMI participants.

Furthermore, the primary endpoint was analysed by a core lab blinded to both the treatment and the clinical data, therefore the double-blind design was not considered necessary.

Number of subjects in period 1	PPCI with Bivalirudin	PPCI with Heparin
Started	38	40
Per-Protocol Population	28 [2]	36 [3]
Received Study Drug	38	40
Completed	32	37
Not completed	6	3
Adverse event, serious fatal	1	1
Consent withdrawn by subject	5	1
Lost to follow-up	-	1

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The Per-Protocol (PP) population was defined as all enrolled participants in the randomised trial who underwent successful PPCI defined as TIMI Flow of 2 or 3, underwent CMR at 5 days, and were without major protocol deviations. A total of 64 participants (28 in the Bivalirudin Arm and 36 in the UFH Arm) were included in the PP population. The primary and secondary analyses were based on the PP population.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The PP population was defined as all enrolled participants in the randomised trial who underwent successful PPCI defined as thrombolysis in myocardial infarction (TIMI) Flow of 2 or 3, underwent CMR at 5 days, and were without major protocol deviations. A total of 64 participants (28 in the Bivalirudin Arm and 36 in the UFH Arm) were included in the PP population. The primary and secondary analyses were based on the PP population.

Baseline characteristics

Reporting groups	
Reporting group title	PPCI with Bivalirudin
Reporting group description:	
Bivalirudin was administered as a bolus (0.75 milligram [mg]/kilogram [kg]) and an infusion (1.75 mg/kg/h) for the duration of the PPCI and continued for the first 4 h after completion of the procedure.	
Reporting group title	PPCI with Heparin
Reporting group description:	
UFH administered as a bolus according to standard of care for completion of PPCI per site. An activated clotting time (ACT) ≥250 seconds (s) at the end of the procedure was recommended.	

Reporting group values	PPCI with Bivalirudin	PPCI with Heparin	Total
Number of subjects	38	40	78
Age categorical			
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)	22	26	48
From 65-84 years	14	12	26
85 years and over	2	2	4
Age continuous			
Units: years			
arithmetic mean	63.6	61.2	
standard deviation	± 11.4	± 13.2	-
Gender categorical			
Units: Subjects			
Female	10	6	16
Male	28	34	62

End points

End points reporting groups

Reporting group title	PPCI with Bivalirudin
Reporting group description:	
Bivalirudin was administered as a bolus (0.75 milligram [mg]/kilogram [kg]) and an infusion (1.75 mg/kg/h) for the duration of the PPCI and continued for the first 4 h after completion of the procedure.	
Reporting group title	PPCI with Heparin
Reporting group description:	
UFH administered as a bolus according to standard of care for completion of PPCI per site. An activated clotting time (ACT) ≥250 seconds (s) at the end of the procedure was recommended.	
Subject analysis set title	Safety Population (Received Study Drug)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Population includes all enrolled participants who received either bivalirudin or UFH.	
Subject analysis set title	PP Population
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population includes all enrolled participants who underwent successful PPCI and Day-5 CMR without major protocol deviations.	
Subject analysis set title	Intent-to-Treat (ITT) Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population includes all patients enrolled into the randomised trial. Analyses based on the ITT population were considered secondary and confirmatory.	

Primary: CMR Assessment of Infarct Size At Day 5

End point title	CMR Assessment of Infarct Size At Day 5
End point description:	
Size of cardiac infarct, expressed as grams, as assessed by CMR. The use of CMR has dramatically improved the ability for accurate infarct size estimations and is therefore currently considered the gold standard. The number of participants and their mean reported infarct size, as grams, at Day 5 are presented.	
End point type	Primary
End point timeframe:	
5 days post PPCI	

End point values	PPCI with Bivalirudin	PPCI with Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[1]	36[2]		
Units: Grams				
arithmetic mean (standard deviation)	25 (± 19.7)	27.1 (± 20.7)		

Notes:

[1] - PP Population (enrolled participants with successful PPCI and CMR).

[2] - PP Population (enrolled participants with successful PPCI and CMR).

Statistical analyses

Statistical analysis title	Statistical Analysis: CMR Assessment of Infarct
Comparison groups	PPCI with Bivalirudin v PPCI with Heparin
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7505
Method	Wilcoxon rank sum test

Secondary: CMR Assessment Of Myocardial Salvage Index (MSI) At Day 5

End point title	CMR Assessment Of Myocardial Salvage Index (MSI) At Day 5

End point description:

MSI is a CMR-derived parameter of myocardial recovery and treatment efficacy that allows comparisons among infarcts of different sizes. MSI is calculated as the difference between the area at risk (AAR) and the final infarct size, divided by the AAR, and it is expressed as a percentage of AAR. The number of participants and their mean-reported MSI at Day 5 are presented.

End point type	Secondary

End point timeframe:

5 days post PPCI

End point values	PPCI with Bivalirudin	PPCI with Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[3]	15[4]		
Units: Percentage of AAR				
arithmetic mean (standard deviation)	39.4 (± 19.3)	51.2 (± 21.7)		

Notes:

[3] - Per-Protocol Population and participants with a successful CMR assessment of MSI.

[4] - Per-Protocol Population and participants with a successful CMR assessment of MSI.

Statistical analyses

No statistical analyses for this end point

Secondary: CMR Assessment Of Micro-vascular Obstruction (MVO) At Day 5

End point title	CMR Assessment Of Micro-vascular Obstruction (MVO) At Day 5

End point description:

Early and late assessment of MVO, expressed as grams, as assessed by CMR. MVO is an established complication of coronary reperfusion therapy for acute myocardial infarction. MVO occurs in the setting of reperfusion following prolonged myocardial ischemia and provides incremental prognostic information beyond infarct size, to which it is related. The number of participants and their mean reported MVO, as grams, at Day 5 are presented.

End point type	Secondary

End point timeframe:

5 days post PPCI

End point values	PPCI with Bivalirudin	PPCI with Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[5]	35[6]		
Units: Grams				
arithmetic mean (standard deviation)				
CMR Early MVO Assessment	5.3 (± 5.8)	7.7 (± 6.3)		
CMR Late MVO Assessment	3.7 (± 5.7)	4.2 (± 4.5)		

Notes:

[5] - Per-Protocol Population and participants with successful CMR assessment of Early (23)/Late (27) MVO.

[6] - Per-Protocol Population and participants with successful CMR assessment of Early (28)/Late (35) MVO.

Statistical analyses

No statistical analyses for this end point

Secondary: CMR Assessment Of Left Ventricular Ejection Fraction (LVEF) At Day 5

End point title	CMR Assessment Of Left Ventricular Ejection Fraction (LVEF) At Day 5

End point description:

Percentage of cardiac LVEF as assessed by CMR. LVEF is a measurement of the percentage of blood ejected out of the left ventricle with each contraction. The number of participants and their mean reported LVEF, as a percentage of blood, at Day 5 are presented.

End point type	Secondary

End point timeframe:

5 days post PPCI

End point values	PPCI with Bivalirudin	PPCI with Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[7]	36[8]		
Units: Percentage of Blood				
arithmetic mean (standard deviation)	48.5 (± 11)	48.6 (± 10.9)		

Notes:

[7] - Per-Protocol Population (enrolled participants with successful PPCI and CMR).

[8] - Per-Protocol Population (enrolled participants with successful PPCI and CMR).

Statistical analyses

No statistical analyses for this end point

Secondary: CMR Assessment of LVEF at Day 90

End point title	CMR Assessment of LVEF at Day 90

End point description:

Percentage of cardiac LVEF as assessed by CMR. LVEF is a measurement of the percentage of blood ejected out of the left ventricle with each contraction. The number of participants and their mean reported LVEF, as a percentage of blood, at Day 90 are presented.

End point type	Secondary

End point timeframe:

90 days post PPCI

End point values	PPCI with Bivalirudin	PPCI with Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[9]	29[10]		
Units: Percentage of Blood				
arithmetic mean (standard deviation)	54.6 (± 12)	49.1 (± 12.1)		

Notes:

[9] - Per-Protocol Population and participants with a successful CMR assessment of LVEF at Day 90.

[10] - Per-Protocol Population and participants with a successful CMR assessment of LVEF at Day 90.

Statistical analyses

No statistical analyses for this end point

Secondary: TIMI Flow and Myocardial Blush Grade (MBG) at End of PPCI

End point title	TIMI Flow and Myocardial Blush Grade (MBG) at End of PPCI

End point description:

TIMI flow (grade 0-3) is an angiographic determination of briskness of epicardial coronary blood flow: TIMI 0 flow (no perfusion); TIMI 1 flow (penetration without perfusion); TIMI 2 flow (partial reperfusion); TIMI 3 flow (complete perfusion/normal flow).
MBG (grade 0-3) is an angiographic method for determination of blood flow in the distal myocardial vascular bed. Blush grades: 0 = failure of dye to enter the microvasculature; 1 = dye slowly enters but fails to exit the microvasculature; 2 = delayed entry and exit of dye from the microvasculature; 3 = normal entry and exit of dye from the microvasculature. Blush that is only mildly intense throughout the washout phase, but fades minimally, is also classified as grade 3.
The number of participants and their mean reported TIMI flow and MBG grades at the end of PPCI are presented.

End point type	Secondary

End point timeframe:

1 day (end of PPCI)

End point values	PPCI with Bivalirudin	PPCI with Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[11]	36[12]		
Units: Grade				
arithmetic mean (standard deviation)				
TIMI Flow Grade	2.8 (± 0.4)	2.8 (± 0.4)		
MBG	1.8 (± 1.2)	1.5 (± 1.2)		

Notes:

[11] - Per-Protocol Population and participants with a TIMI Flow (28) and MBG (22) at the end of PPCI.

[12] - Per-Protocol Population and participants with a TIMI Flow (36) and MBG (29) at the end of PPCI.

Statistical analyses

No statistical analyses for this end point

Secondary: In-Hospital Net Adverse Cardiac Events (NACE) At Day 5

End point title	In-Hospital Net Adverse Cardiac Events (NACE) At Day 5

End point description:

The NACE at 5 days is the composite of major bleeding (Bleeding Academic Research Consortium Type 3 or greater [BARC type ≥3]), death, re-infarction, and ischaemia driven revascularization (IDR).
In brief, BARC ≥3 includes: Type 3a-3c, clinical, laboratory, and/or imaging evidence of bleeding; Type 4, coronary artery bypass grafting-related bleeding; Type 5, fatal bleeding that directly results in death that is either clinically suspicious or is confirmed as the cause of death.
A participant was defined to have a composite event if the participant experienced at least 1 of the components. If the participant did not have any of the components, then he or she did not have the composite endpoint. If a participant had more than 1 of the components, he or she was only counted once in the determination of the total number of participants experiencing the composite endpoint. The number of participants with NACE up to Day 5 is presented.

End point type	Secondary

End point timeframe:

5 days post PPCI or at discharge, whichever occurs first

End point values	PPCI with Bivalirudin	PPCI with Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[13]	36[14]		
Units: Percentage of participants				
number (not applicable)	7.1	8.3		

Notes:

[13] - Per-Protocol Population (enrolled participants with successful PPCI and CMR).

[14] - Per-Protocol Population (enrolled participants with successful PPCI and CMR).

Statistical analyses

No statistical analyses for this end point

Secondary: Death At Day 90

End point title	Death At Day 90

End point description:

Participant survival during the clinical follow-up period is presented as the number of participants with reported death at 90 days post PPCI.

End point type	Secondary

End point timeframe:

90 days post PPCI

End point values	PPCI with Bivalirudin	PPCI with Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[15]	36[16]		
Units: Participants	0	1		

Notes:

[15] - Per-Protocol Population (enrolled participants with successful PPCI and CMR).

[16] - Per-Protocol Population (enrolled participants with successful PPCI and CMR).

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Index Of Microcirculatory Resistance (IMR)

End point title	Index Of Microcirculatory Resistance (IMR)

End point description:

IMR, a predictor of clinical outcome, is a readily available, quantitative, and reproducible method for invasively assessing coronary microvascular function. It is measured using the thermodilution technique and expressed as millimeters (mm) of mercury (Hg) multiplied by the mean hyperemic transit time (s) (mmHg·s). The number of participants and their mean reported IMR at the end of PPCI are presented.

End point type	Other pre-specified

End point timeframe:

1 day (end of PPCI)

End point values	PPCI with Bivalirudin	PPCI with Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[17]	25[18]		
Units: mmHg·s				
arithmetic mean (standard deviation)	43.49 (± 21.62)	68.66 (± 35.77)		

Notes:

[17] - IMR ITT population.

[18] - IMR ITT population.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 5 days (±36 h) post randomisation/discharge	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	PPCI with Bivalirudin
Reporting group description:	
Bivalirudin was administered as a bolus (0.75 mg/kg) and an infusion (1.75 mg/kg/h) for the duration of the PPCI and continued for the first 4 h after completion of the procedure.	
Reporting group title	PPCI with Heparin
Reporting group description:	
UFH was administered as a bolus according to standard of care for completion of PPCI per site. An ACT ≥250 s at the end of the procedure was recommended.	

Serious adverse events	PPCI with Bivalirudin	PPCI with Heparin	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 38 (15.79%)	7 / 40 (17.50%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events			
Cardiac disorders			
Cardiogenic shock			
subjects affected / exposed	2 / 38 (5.26%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 38 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac asthma			
subjects affected / exposed	0 / 38 (0.00%)	1 / 40 (2.50%)	
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 / 38 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 38 (2.63%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery perforation			
subjects affected / exposed	1 / 38 (2.63%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial rupture			
subjects affected / exposed	1 / 38 (2.63%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 38 (2.63%)	0 / 40 (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			
Transient ischaemic attack			
subjects affected / exposed	1 / 38 (2.63%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	0 / 38 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 38 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	PPCI with Bivalirudin	PPCI with Heparin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 38 (28.95%)	6 / 40 (15.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 38 (2.63%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Phlebitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 38 (5.26%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Ventricular tachycardia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Bradycardia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Ventricular arrhythmia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			

Drug hypersensitivity			
subjects affected / exposed	1 / 38 (2.63%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 38 (2.63%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 38 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 38 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Lung disorder			
subjects affected / exposed	1 / 38 (2.63%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 38 (2.63%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Nephropathy toxic			
subjects affected / exposed	0 / 38 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Renal failure			
subjects affected / exposed	1 / 38 (2.63%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Urinary retention			
subjects affected / exposed	0 / 38 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 38 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Infections and infestations			

Pneumonia subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	0 / 40 (0.00%) 0	
Metabolism and nutrition disorders Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 40 (2.50%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2015	Amendment number 1 on 24-August-2015 included the following clinical changes to the protocol: - An interim analysis was added to the protocol. The proposed interim analysis was performed to assess the assumptions used to evaluate the scientific validity of the hypothesis tested, and how this was affected by protocol deviations impacting the sensitive tool used to assess the infarct size (CMR). It was planned when approximately 66 evaluable participants (a third of the planned sample size) had their day 5 CMR data available for analysis. - Changes were made to clarify clinical intent: in particular changes to the primary and secondary objectives, schedule and sequence of procedures and protocol deviations. - Updates were made to ensure consistency throughout the protocol: in particular updates to the synopsis, Type/Design of Trial, Number of Subjects, schedule and sequence of procedures, and sample size. - Other changes were made, including: - addition of a new section, Reporting Events of Medication Errors, to clarify definition of medication errors and explain how to report them; - addition of a new section, Screen Failures has been added to explain the procedure used, to account for screening failures. These proposed changes were considered substantial but did not affect the benefit–risk assessment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Since the measured difference in infarct size at Day 5 (by CMR) was <18%, the study was terminated for futility at the interim analysis as pre-defined in the protocol.

Notes: