Clinical trial results:
Multi-centre, multi-national, prospective, randomised, open-label, comparison of bivalirudin to other guideline based current therapies (excluding bivalirudin)

Summary

EudraCT number	2008-007290-20
Trial protocol	DE AT DK FR NL CZ ES PL IT SI
Global end of trial date	01 August 2014

Results information

Result version number	v1 (current)
This version publication date	22 May 2016
First version publication date	22 May 2016

Trial information

Trial identification

Sponsor protocol code	TMC-BIV-08-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01087723
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Medicines Company
Sponsor organisation address	8 Sylvan Way, Parsippany, United States,
Public contact	Global Health Science Center, The Medicines Company, 41044 800-388-1183, medical.information@themedco.com.us
Scientific contact	Global Health Science Center, The Medicines Company, 41044 800-388-1183, medical.information@themedco.com.us

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	01 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 August 2013
Global end of trial reached?	Yes
Global end of trial date	01 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To show that the early administration of bivalirudin improves 30-day outcomes when compared to the current standard of care in participants with ST segment elevation acute coronary syndrome (STE-ACS), intended for a primary percutaneous coronary intervention (PCI) management strategy, presenting either via ambulance or to centers where PCI is not performed.

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	01 March 2010
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	Czech Republic: 1
Country: Number of subjects enrolled	Netherlands: 768
Country: Number of subjects enrolled	Denmark: 150
Country: Number of subjects enrolled	Poland: 111
Country: Number of subjects enrolled	Italy: 72
Country: Number of subjects enrolled	France: 795
Country: Number of subjects enrolled	Germany: 279
Country: Number of subjects enrolled	Slovenia: 13
Country: Number of subjects enrolled	Austria: 9
Worldwide total number of subjects	2198
EEA total number of subjects	2198

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)	1310
From 65 to 84 years	801
85 years and over	87

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The decision to randomize participants was made by a qualified physician or paramedic who was present at the time. Participants were included in the study if they presented either via ambulance or to a center where PCI was not performed and met inclusion criteria.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Bivalirudin

Arm description:

Given immediately upon enrolment as an intravenous (IV) bolus of 0.75 milligrams/kilogram (mg/kg), followed immediately by an infusion of 1.75 mg/kg/hour (mg/kg/h). This infusion was to be run continuously until completion of percutaneous coronary intervention (PCI), at which time the infusion was reduced to 0.25 mg/kg/h for at least 4 hours. An optional PCI-dose infusion of 1.75 mg/kg/h was also permitted for up to 4 hours at the discretion of the operator.

Arm type	Experimental
Investigational medicinal product name	Bivalirudin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Intravenous use

Dosage and administration details:

Given immediately upon enrollment as an intravenous (IV) bolus of 0.75 mg/kilogram (mg/kg), followed immediately by an infusion of 1.75 mg/kg/hour (mg/kg/h). This infusion was to be run continuously until completion of PCI, at which time the infusion was reduced to 0.25 mg/kg/h for at least 4 hours. An optional PCI-dose infusion of 1.75 mg/kg/h was also permitted for up to 4 hours at the discretion of the operator.

Arm title	Standard of Care: Heparins with optional GPI

Arm description:

Standard-of-care anti-thrombotic therapy as outlined in the European Society of Cardiology Dosing Guidelines for Management of ST segment elevation acute coronary syndrome (STE-ACS), not including bivalirudin: unfractionated heparin (UFH) (100 international units/kg [IU/kg] without glycoprotein IIb/IIIa inhibitor [GPI] and 60 IU/kg with GPI). Any of the following approved GPIs were used either as a routine strategy or as a bail out: eptifibatide (two 180-micrograms/kilogram [µg/kg] IV boluses with a 10-minute [min] interval followed by an infusion of 2.0 µg/kg/min for 72-96 hours); tirofiban (25 µg/kg followed by an infusion of 0.15 µg/kg/min for 18-24 hours); or abciximab (bolus of 0.25 mg/kg followed by an infusion of 0.125 µg/kg/min for 12-24 hours [maximum dose of 10 µg/min]).

For this study, the control consisted of treatment with UFH or low molecular weight heparin (LMWH) with or without GPI and is referred to as "heparins with optional GPI.”

Arm type	Active comparator
Investigational medicinal product name	Standard of Care: Heparins with Optional GPI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Intravenous use

Dosage and administration details:

Standard-of-care anti-thrombotic therapy as outlined in the European Society of Cardiology Dosing Guidelines for Management of STE-ACS, not including bivalirudin: UFH (100 international units/kg [IU/kg] without GPI and 60 IU/kg with GPI). Any of the following approved GPIs were used either as a routine strategy or as a bail out: eptifibatide (two 180-micrograms/kilogram [µg/kg] IV boluses with a 10-minute [min] interval followed by an infusion of 2.0 µg/kg/min for 72-96 hours); tirofiban (25 µg/kg followed by an infusion of 0.15 µg/kg/min for 18-24 hours); or abciximab (bolus of 0.25 mg/kg followed by an infusion of 0.125 µg/kg/min for 12-24 hours [maximum dose of 10 µg/min]).
For this study, the control consisted of treatment with UFH or low molecular weight heparin (LMWH) with or without GPI and is referred to as "heparins with optional GPI."

Number of subjects in period 1	Bivalirudin	Standard of Care: Heparins with optional GPI
Started	1089	1109
Received at least 1 dose of study drug	1089	1094
Additional by treatment received	10 [1]	0 [2]
Completed	1075	1089
Not completed	14	20
Physician decision	2	-
Consent withdrawn by subject	10	13
1 Year Visit Too Early (<335 days)	-	1
Reason Not Specified	1	2
Lost to follow-up	1	4

Notes:

[1] - 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: A total of 1089 participants were randomized and signed an informed consent form (ICF). This represents the Intent-to-treat (ITT) population. A total of 1099 participants were randomized with signed ICFs and who actually received this treatment (bivalirudin). This cohort represents the as-treated Safety population.

[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: No additional participants were randomized and signed an informed consent form (ICF). The as-treated Safety population is consistent with the number of participants that received at least 1 dose of study drug for this treatment arm (standard of care: heparins with optional GPI).

Baseline characteristics

Reporting groups	
Reporting group title	Bivalirudin

Reporting group description:

Given immediately upon enrolment as an intravenous (IV) bolus of 0.75 milligrams/kilogram (mg/kg), followed immediately by an infusion of 1.75 mg/kg/hour (mg/kg/h). This infusion was to be run continuously until completion of percutaneous coronary intervention (PCI), at which time the infusion was reduced to 0.25 mg/kg/h for at least 4 hours. An optional PCI-dose infusion of 1.75 mg/kg/h was also permitted for up to 4 hours at the discretion of the operator.

Reporting group title	Standard of Care: Heparins with optional GPI

Reporting group description:

Standard-of-care anti-thrombotic therapy as outlined in the European Society of Cardiology Dosing Guidelines for Management of ST segment elevation acute coronary syndrome (STE-ACS), not including bivalirudin: unfractionated heparin (UFH) (100 international units/kg [IU/kg] without glycoprotein IIb/IIIa inhibitor [GPI] and 60 IU/kg with GPI). Any of the following approved GPIs were used either as a routine strategy or as a bail out: eptifibatide (two 180-micrograms/kilogram [µg/kg] IV boluses with a 10-minute [min] interval followed by an infusion of 2.0 µg/kg/min for 72-96 hours); tirofiban (25 µg/kg followed by an infusion of 0.15 µg/kg/min for 18-24 hours); or abciximab (bolus of 0.25 mg/kg followed by an infusion of 0.125 µg/kg/min for 12-24 hours [maximum dose of 10 µg/min]).

For this study, the control consisted of treatment with UFH or low molecular weight heparin (LMWH) with or without GPI and is referred to as "heparins with optional GPI."

Reporting group values	Bivalirudin	Standard of Care: Heparins with optional GPI	Total
Number of subjects	1089	1109	2198
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age Continuous Units: years			
arithmetic mean	61.4	62	
standard deviation	± 12.8	± 13.1	-
Gender, Male/Female Units: participants			
Female	275	248	523
Male	814	861	1675
Region of Enrollment Units: Subjects			
Austria	4	5	9
Czech Republic	0	1	1
Netherlands	377	391	768

Denmark	78	72	150
Poland	55	56	111
Italy	31	41	72
France	398	397	795
Germany	139	140	279
Slovenia	7	6	13
Medical history: Participant Has Diabetes Units: Subjects			
Yes	127	169	296
No	962	940	1902
Medical history: Participant Is a Current Smoker (within past 30 days) Units: Subjects			
Yes	453	472	925
No	636	637	1273
Medical history: Participant Has Hypertension Units: Subjects			
Yes	459	504	963
No	630	605	1235
Medical history: Participant Has Hyperlipidemia			
Participant has known hyperlipidemia or is on lipid-lowering drugs			
Units: Subjects			
Yes	398	417	815
No	691	692	1383
Medical history: Participant Has Had Previous Myocardial Infarction (MI) Units: Subjects			
Yes	80	113	193
No	1009	996	2005

End points

End points reporting groups

Reporting group title	Bivalirudin

Reporting group description:

Given immediately upon enrolment as an intravenous (IV) bolus of 0.75 milligrams/kilogram (mg/kg), followed immediately by an infusion of 1.75 mg/kg/hour (mg/kg/h). This infusion was to be run continuously until completion of percutaneous coronary intervention (PCI), at which time the infusion was reduced to 0.25 mg/kg/h for at least 4 hours. An optional PCI-dose infusion of 1.75 mg/kg/h was also permitted for up to 4 hours at the discretion of the operator.

Reporting group title	Standard of Care: Heparins with optional GPI

Reporting group description:

Standard-of-care anti-thrombotic therapy as outlined in the European Society of Cardiology Dosing Guidelines for Management of ST segment elevation acute coronary syndrome (STE-ACS), not including bivalirudin: unfractionated heparin (UFH) (100 international units/kg [IU/kg] without glycoprotein IIb/IIIa inhibitor [GPI] and 60 IU/kg with GPI). Any of the following approved GPIs were used either as a routine strategy or as a bail out: eptifibatide (two 180-micrograms/kilogram [µg/kg] IV boluses with a 10-minute [min] interval followed by an infusion of 2.0 µg/kg/min for 72-96 hours); tirofiban (25 µg/kg followed by an infusion of 0.15 µg/kg/min for 18-24 hours); or abciximab (bolus of 0.25 mg/kg followed by an infusion of 0.125 µg/kg/min for 12-24 hours [maximum dose of 10 µg/min]).

For this study, the control consisted of treatment with UFH or low molecular weight heparin (LMWH) with or without GPI and is referred to as "heparins with optional GPI.”

Primary: The Composite Incidence of Death and Non-coronary Artery Bypass Graft (CABG) Major Bleeding

End point title	The Composite Incidence of Death and Non-coronary Artery Bypass Graft (CABG) Major Bleeding

End point description:

A participant was defined to have had a composite event if the participant experienced at least 1 of the 2 components (death or non-CABG major bleeding) of the composite. Incidence=the number of participants to experience the event/total number of at risk participants x 100. Death was defined as death from any cause at any time. Non-CABG major bleeding was defined as any 1 of the following: intra-cranial, retroperitoneal, intraocular, access site hemorrhage requiring radiological or surgical intervention, reduction in hemoglobin (Hb) concentration of >4 grams/deciliter (g/dL) without an overt source of bleeding, reduction in hemoglobin concentration of >3 g/dL with an overt source of bleeding; re-intervention for bleeding, or use of any blood product transfusion.

End point type	Primary

End point timeframe:

Within 30 days

End point values	Bivalirudin	Standard of Care: Heparins with optional GPI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1089	1109		
Units: percentage of participants				
number (not applicable)	5.1	8.5		

Statistical analyses

Statistical analysis title	Bivalirudin, Standard of Care 1
Comparison groups	Bivalirudin v Standard of Care: Heparins with optional GPI
Number of subjects included in analysis	2198
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0014
Method	Chi-squared
Parameter estimate	Relative Risk
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.82

Secondary: The Composite Incidence of Death, Re-infarction (MI), or Non-CABG Major Bleeding

End point title	The Composite Incidence of Death, Re-infarction (MI), or Non-CABG Major Bleeding

End point description:

A participant had a composite event if the participant experienced at least 1 of the 3 components (death, re-infarction [MI], or non-CABG major bleeding) of the composite. Incidence=the number of participants to experience the event/total number of at risk participants x 100. Death was defined as death from any cause at any time. Non-CABG major bleeding was defined as any one of the following: intracranial, retroperitoneal, intraocular, access site hemorrhage requiring radiological or surgical intervention, reduction in Hb concentration of >4 g/dL without an overt source of bleeding, reduction in hemoglobin concentration of >3 g/dL with an overt source of bleeding, re-intervention for bleeding, use of any blood product transfusion. MI was defined as a positive diagnosis of re-infarction (new event) not associated with index PCI. This was originally the study primary endpoint. The second protocol amendment (dated 24 April 2012) re-categorized this as a key secondary outcome.

End point type	Secondary

End point timeframe:

Within 30 days

End point values	Bivalirudin	Standard of Care: Heparins with optional GPI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1089	1109		
Units: percentage of participants				
number (not applicable)	6.6	9.2		

Statistical analyses

Statistical analysis title	Bivalirudin, Standard of Care 2
Comparison groups	Bivalirudin v Standard of Care: Heparins with optional GPI
Number of subjects included in analysis	2198
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.02
Method	Chi-squared
Parameter estimate	Relative Risk
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.96

Secondary: The Incidence of Death, Re-infarction, Non-CABG-related Major Bleeding, or Ischemia-driven Revascularization (IDR)

End point title	The Incidence of Death, Re-infarction, Non-CABG-related Major Bleeding, or Ischemia-driven Revascularization (IDR)

End point description:

Incidence=number of participants to experience the event/total number of at risk participants x 100. Death from any cause at any time. Re-infarction was a positive diagnosis of re-infarction not associated with index PCI. Non-CABG major bleeding was any 1 of: intracranial, retroperitoneal, intraocular, access site hemorrhage requiring radiological or surgical intervention, reduction in Hb concentration of >4 g/dL without an overt source of bleeding, reduction in hemoglobin concentration of >3 g/dL with an overt source of bleeding, re-intervention for bleeding, use of any blood product transfusion. IDR was any refractory ischemia-driven repeat percutaneous intervention or bypass graft surgery involving any native coronary or pre-existing bypass graft vessel. In the absence of pain, new ST segment changes indicative of ischemia, acute pulmonary edema, ventricular arrhythmias, or hemodynamic instability presumed to be ischemic in origin, will constitute sufficient evidence of ischemia.

End point type	Secondary

End point timeframe:

Within 30 days

End point values	Bivalirudin	Standard of Care: Heparins with optional GPI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1089	1109		
Units: percentage of participants				
number (not applicable)				
Death	2.9	3.1		
Re-infarction	1.7	0.9		
Non-CABG-related major bleeding	2.6	6		
IDR	2.2	1.5		

Statistical analyses

No statistical analyses for this end point

Secondary: The Incidence of Death at 1 Year

End point title	The Incidence of Death at 1 Year

End point description:

Incidence=the number of participants to experience the event/total number of at risk participants x 100. Death was defined as death from any cause at any time.

End point type	Secondary

End point timeframe:

Within 1 Year

End point values	Bivalirudin	Standard of Care: Heparins with optional GPI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1089	1109		
Units: percentage of participants				
number (not applicable)	5.4	5.3		

Statistical analyses

No statistical analyses for this end point

Secondary: The Incidence of Major bleeding: Thrombolysis in MI (TIMI) and Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO)

End point title	The Incidence of Major bleeding: Thrombolysis in MI (TIMI) and Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO)

End point description:

Incidence=the number of participants to experience the event/total number of at risk participants x 100. Major bleeding based on TIMI criteria was defined as any intra-cranial bleeding, or any bleeding associated with clinically overt signs associated with a drop in Hb of >5 g/dL (or, when Hb was not available, an absolute drop in hematocrit [Hct] >15%). Major bleeding based on GUSTO criteria was defined as severe/life-threatening: intra-cranial hemorrhage or resulting in substantial hemodynamic compromise requiring treatment.

End point type	Secondary

End point timeframe:

Within 30 days

End point values	Bivalirudin	Standard of Care: Heparins with optional GPI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1089	1109		
Units: percentage of participants				
number (not applicable)				
Major bleeding: TIMI	1.3	2.1		
Major bleeding: GUSTO	1.3	2.3		

Statistical analyses

No statistical analyses for this end point

Secondary: The Incidence of Minor Bleeding: TIMI and GUSTO

End point title	The Incidence of Minor Bleeding: TIMI and GUSTO

End point description:

Incidence=the number of participants to experience the event/total number of at risk participants x 100. Minor bleeding based on TIMI criteria was defined as any clinically overt sign of bleeding (including observation by imaging techniques) that was associated with a fall in Hb of ≥3 g/dL and ≤5 g/dL (or, when Hb was not available, an absolute drop in Hct of ≥9% and ≤15%). Minor bleeding based on GUSTO criteria was defined as other bleed not requiring blood transfusion or causing hemodynamic compromise.

End point type	Secondary

End point timeframe:

Within 30 days

End point values	Bivalirudin	Standard of Care: Heparins with optional GPI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1089	1109		
Units: percentage of participants				
number (not applicable)				
Minor bleeding: TIMI	6.5	11.2		
Minor bleeding: GUSTO	6.5	11		

Statistical analyses

No statistical analyses for this end point

Secondary: The Incidence of Stent Thrombosis (Academic Research Consortium [ARC definition])

End point title	The Incidence of Stent Thrombosis (Academic Research Consortium [ARC definition])

End point description:

Incidence=the number of participants to experience the event/total number of at risk participants x 100. Stent thrombosis, based on the ARC definition, was defined as angiographic confirmation of stent thrombosis, non-occlusive thrombus, occlusive thrombus, or pathological confirmation of stent thrombosis.

End point type	Secondary

End point timeframe:

Within 30 days

End point values	Bivalirudin	Standard of Care: Heparins with optional GPI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1089	1109		
Units: percentage of participants				
number (not applicable)	1.6	0.5		

Statistical analyses

No statistical analyses for this end point

Secondary: The Incidence of Thrombocytopenia

End point title	The Incidence of Thrombocytopenia

End point description:

Incidence=the number of participants to experience the event/total number of at risk participants x 100. Thrombocytopenia was defined as a post-procedural platelet count <100,000 cells/millimeter cubed (cells/mm^3) in a participant with a baseline or pre-procedural platelet count >100,000 cells/mm^3.

End point type	Secondary

End point timeframe:

Within 30 days

End point values	Bivalirudin	Standard of Care: Heparins with optional GPI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1089	1109		
Units: percentage of participants				
number (not applicable)	0.7	1.4		

Statistical analyses

No statistical analyses for this end point

Secondary: The Incidence of Stroke

End point title	The Incidence of Stroke

End point description:

Incidence=the number of participants to experience the event/total number of at risk participants x 100. Stroke was defined as a sudden, focal neurological defect resulting from a cerebrovascular cause, resulting in death or lasting greater than 24 hours that was not due to a readily identifiable cause, such as a tumor, infection, or trauma.

End point type	Secondary

End point timeframe:

Within 30 days

End point values	Bivalirudin	Standard of Care: Heparins with optional GPI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1089	1109		
Units: percentage of participants				
number (not applicable)	0.6	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening to Day 30

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Standard of Care: Heparins with optional GPI

Reporting group description:

Standard-of-care anti-thrombotic therapy as outlined in the European Society of Cardiology Dosing Guidelines for Management of STE-ACS, not including bivalirudin: UFH (100 international IU/kg without GPI and 60 IU/kg with GPI). Any of the following approved GPIs were used either as a routine strategy or as a bail out: eptifibatide (two 180-µg/kg IV boluses with a 10-min interval followed by an infusion of 2.0 µg/kg/min for 72-96 hours); tirofiban (25 µg/kg followed by an infusion of 0.15 µg/kg/min for 18-24 hours); or abciximab (bolus of 0.25 mg/kg followed by an infusion of 0.125 µg/kg/min for 12-24 hours [maximum dose of 10 µg/min]).

For this study, the control consisted of treatment with UFH or LMWH with or without GPI and is referred to as "heparins with optional GPI."

Reporting group title	Bivalirudin

Reporting group description:

Given immediately upon enrollment as an IV bolus of 0.75 mg/kg, followed immediately by an infusion of 1.75 mg/kg/h. This infusion was to be run continuously until completion of PCI, at which time the infusion was reduced to 0.25 mg/kg/h for at least 4 hours. An optional PCI-dose infusion of 1.75 mg/kg/h was also permitted for up to 4 hours at the discretion of the operator.

Serious adverse events	Standard of Care: Heparins with optional GPI	Bivalirudin	
Total subjects affected by serious adverse events			
subjects affected / exposed	129 / 1094 (11.79%)	145 / 1099 (13.19%)	
number of deaths (all causes)	32	33	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasmacytoma			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic neoplasm			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Abdominal neoplasm			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 1094 (0.00%)	4 / 1099 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 1094 (0.18%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	1 / 1094 (0.09%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reperfusion injury			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm rupture			
subjects affected / exposed	0 / 1094 (0.00%)	2 / 1099 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemodynamic instability			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			

subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	0 / 1094 (0.00%)	3 / 1099 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chest pain			
subjects affected / exposed	3 / 1094 (0.27%)	5 / 1099 (0.45%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 1094 (0.09%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 1094 (0.09%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sudden cardiac death			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malaise			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac death			

subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	5 / 1094 (0.46%)	3 / 1099 (0.27%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary oedema			
subjects affected / exposed	1 / 1094 (0.09%)	2 / 1099 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 1094 (0.09%)	2 / 1099 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 1094 (0.09%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	2 / 1094 (0.18%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 1094 (0.09%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Orthopnoea			

subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Hallucination			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Arteriogram coronary			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
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			
Gastrointestinal injury			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Facial bones fracture			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Ventricular septal defect			

subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Ventricular fibrillation			
subjects affected / exposed	28 / 1094 (2.56%)	39 / 1099 (3.55%)	
occurrences causally related to treatment / all	0 / 32	2 / 40	
deaths causally related to treatment / all	0 / 3	0 / 1	
Cardiogenic shock			
subjects affected / exposed	17 / 1094 (1.55%)	21 / 1099 (1.91%)	
occurrences causally related to treatment / all	0 / 17	0 / 21	
deaths causally related to treatment / all	0 / 6	0 / 10	
Cardiac arrest			
subjects affected / exposed	17 / 1094 (1.55%)	7 / 1099 (0.64%)	
occurrences causally related to treatment / all	0 / 18	0 / 7	
deaths causally related to treatment / all	0 / 8	0 / 1	
Cardiac failure			
subjects affected / exposed	10 / 1094 (0.91%)	8 / 1099 (0.73%)	
occurrences causally related to treatment / all	0 / 11	0 / 8	
deaths causally related to treatment / all	0 / 3	0 / 4	
Coronary artery dissection			
subjects affected / exposed	2 / 1094 (0.18%)	7 / 1099 (0.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	4 / 1094 (0.37%)	3 / 1099 (0.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	3 / 1094 (0.27%)	2 / 1099 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			

subjects affected / exposed	2 / 1094 (0.18%)	3 / 1099 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	1 / 1094 (0.09%)	3 / 1099 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	3 / 1094 (0.27%)	2 / 1099 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 1094 (0.18%)	2 / 1099 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery perforation			
subjects affected / exposed	1 / 1094 (0.09%)	2 / 1099 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular septal defect acquired			
subjects affected / exposed	0 / 1094 (0.00%)	2 / 1099 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tachycardia			
subjects affected / exposed	2 / 1094 (0.18%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary no-reflow phenomenon			
subjects affected / exposed	1 / 1094 (0.09%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			

subjects affected / exposed	2 / 1094 (0.18%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 1094 (0.00%)	2 / 1099 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrioventricular block			
subjects affected / exposed	0 / 1094 (0.00%)	2 / 1099 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myocardial infarction			
subjects affected / exposed	2 / 1094 (0.18%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricle rupture			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stress cardiomyopathy			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus arrest			

subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Papillary muscle rupture			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Palpitations			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
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 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mitral valve incompetence			

subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interventricular septum rupture			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorder			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac asthma			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (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	0 / 1094 (0.00%)	2 / 1099 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonia			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Intestinal infarction			
subjects affected / exposed	1 / 1094 (0.09%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ileus			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			

subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haemorrhage			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	4 / 1094 (0.37%)	4 / 1099 (0.36%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Compartment syndrome			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 1094 (0.46%)	2 / 1099 (0.18%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	0 / 1094 (0.00%)	3 / 1099 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Urinary tract infection			
subjects affected / exposed	1 / 1094 (0.09%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	0 / 1094 (0.00%)	1 / 1099 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	1 / 1094 (0.09%)	0 / 1099 (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	Standard of Care: Heparins with optional GPI	Bivalirudin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	119 / 1094 (10.88%)	134 / 1099 (12.19%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	20 / 1094 (1.83%)	22 / 1099 (2.00%)	
occurrences (all)	20	24	
Cardiac disorders			
Ventricular tachycardia			
subjects affected / exposed	39 / 1094 (3.56%)	57 / 1099 (5.19%)	
occurrences (all)	40	62	
Atrial fibrillation			
subjects affected / exposed	35 / 1094 (3.20%)	35 / 1099 (3.18%)	
occurrences (all)	35	36	
Bradycardia			
subjects affected / exposed	25 / 1094 (2.29%)	20 / 1099 (1.82%)	
occurrences (all)	25	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2010	This first protocol amendment, dated 16 April 2010, consisted of both clinical and administrative amendments. The clinical amendments are summarized below. -All endpoints except for mortality were removed from the one-year follow-up assessment. -Stroke was added as a secondary endpoint. -The Health Economics section was removed from the protocol. -Collection of C-reactive protein was removed from the protocol. -The text was clarified to indicate that AE/SAE collection was to commence as soon as consent had been given. -Approval of bivalirudin indication in the European Union (EU) for use in STEMI patients undergoing PCI was added. -Randomisation would only be done using the envelope method rather than a choice of interactive voice response system (IVRS) also.
24 April 2012	This second protocol amendment, dated 24 April 2012, consisted of both clinical and administrative amendments. The clinical amendments are summarized below. -The primary endpoint at 30 days was amended by removing re-infarction (MI). The original primary endpoint was the composite of death from any cause, re-infarction, or non-CABG major bleeding, which became the key secondary outcome after the change in the protocol. The change in the primary endpoint was made to reduce the sample size needed. The treatment effect of bivalirudin was assumed to come entirely from reductions in rates of death or major bleeding, With the anticipated null effect of the two study treatments on re-infarction, the decision to remove this component from the composite primary endpoint substantially reduced trial size to 2,200 subjects (from the initial 3,680 required with the triple composite), a more realistic enrollment goal. -Collection of glucose and HbA1c were removed from the protocol. -Collection of biomarkers 24 and 48 hours post-index procedure was removed from the protocol. -Collection of vital signs was removed from the protocol. An addendum to that amendment was made for Germany as the competent authority in Germany (BfArM) requested that all centres in Germany would continue to perform biomarker and ECG collection at 24 and 48 hours.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported