Clinical trial results:
Effect of Bivalirudin on Aortic Valve Intervention Outcomes 2/3 (BRAVO 2/3)

Summary

EudraCT number	2012-000632-26
Trial protocol	GB DE NL IT
Global end of trial date	24 June 2015

Results information

Result version number	v1 (current)
This version publication date	23 July 2016
First version publication date	23 July 2016

Trial information

Trial identification

Sponsor protocol code	TMC-BIV-11-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01651780
WHO universal trial number (UTN)	-
Other trial identifiers	Clinicaltrials.gov: NCT01651780

Notes:

Sponsors

Sponsor organisation name	The Medicines Company
Sponsor organisation address	8 Sylvan Way, Parsippany, NJ, United States, 07054
Public contact	Global Health Science Center, The Medicines Company, 00800 84363326, medical.information@themedco.com
Scientific contact	Global Health Science Center, The Medicines Company, 00800 84363326, 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	24 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 June 2015
Global end of trial reached?	Yes
Global end of trial date	24 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to assess the safety and efficacy of using bivalirudin instead of unfractionated heparin (UFH) in transcatheter aortic valve replacements (TAVR).
The primary hypothesis of BRAVO 3 was that bivalirudin would reduce major bleeding compared with heparin in TAVR procedures. Results for all particpants enrolled into the randomized trial (BRAVO 3) 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	18 October 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	Canada: 75
Country: Number of subjects enrolled	Switzerland: 47
Country: Number of subjects enrolled	Netherlands: 20
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	France: 214
Country: Number of subjects enrolled	Germany: 353
Country: Number of subjects enrolled	Italy: 76
Worldwide total number of subjects	803
EEA total number of subjects	681

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)	21
From 65 to 84 years	454
85 years and over	328

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening was to take place within 30 days of the start of the study. Screening assessments included review of inclusion/exclusion criteria, signature of informed consent, 12-lead electrocardiogram (ECG), clinical laboratory assessments, measurement of left ventricular ejection fraction (LVEF), and the start of AE or serious AE (SAE) report.

Period 1

Period 1 title	BRAVO 3 (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:

Bivalirudin administered as a bolus and intravenous (IV) infusion. It was recommended that the bolus (0.75 milligrams per kilogram [mg/kg]) be directly administered through the valve delivery sheath immediately following its successful delivery via percutaneous femoral access. Systemic IV administration of the bolus dose was also acceptable. The bivalirudin IV infusion was initiated immediately after the bolus administration. All wires, catheters, and sheaths were to be flushed with heparinized saline.

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 bolus use

Dosage and administration details:

The bivalirudin IV infusion was initiated immediately after the bolus administration at the following doses:
Subjects with normal renal function (glomerular filtration rate [GFR] ≥60 mL/min): 1.75 milligram per kilogram per hour (mg/kg/hr) continuous IV infusion until successful valve treatment was achieved
Subjects with moderate renal impairment (GFR of 30-59 mL/min): 1.4 mg/kg/hr continuous IV infusion until successful valve treatment was achieved
Subjects with severe renal impairment (GFR<30 mL/min): 1.0 mg/kg/hr continuous IV infusion until successful valve treatment was achieved

The GFR was calculated centrally and provided to the investigators during randomization. The IV infusion was to continue until successful valve treatment was achieved. Routine assessment of the activated clotting time (ACT) was not required.

Arm title	Unfractionated heparin (UFH)

Arm description:

The dose of UFH adhered to the standard institutional practice. An ACT target ≥250 seconds was recommended. All wires, catheters, and sheaths were to be flushed with heparinized saline.

Arm type	Active comparator

Investigational medicinal product name	Unfractionated Heparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Intravenous use

Dosage and administration details:

The dose of UFH should adhere to the standard institutional practice. An ACT target ≥ 250 seconds was recommended.

Number of subjects in period 1	Bivalirudin	Unfractionated heparin (UFH)
Started	405	398
Signed consent form (Intent to treat)	404	398
Received at least 1 dose of study drug	393 [1]	394
BRAVO 2 feasibility cohort	65 [2]	0 [3]
Completed	394	388
Not completed	11	10
Consent withdrawn by subject	1	-
Inclusion/Exclusion criteria not met	3	-
Physician decision: Day 30 visit < 23 days	1	5
Did not sign consent form	1	-
Reason not specified: No 30 day visit	2	2
Lost to follow-up	1	2
Physician decision: No 30 day visit	2	1

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: All but one patient in the bivalirudin group (did not sign consent form) comprised the intent-to-treat (ITT) population. In the ITT population, 11 patients in the bivalirudin and four patients in the UFH group did not receive randomized study drug.

[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 first two participants at each site who met inclusion criteria were treated with bivalirudin and comprised the feasibility cohort (BRAVO 2). This cohort was analyzed separately from the randomized trial cohort.

[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 first two participants at each site who met inclusion criteria were treated with bivalirudin and comprised the feasibility cohort (BRAVO 2). This cohort was analyzed separately from the randomized trial cohort and did not include participants treated with UFH.

Baseline characteristics

Reporting groups	
Reporting group title	Bivalirudin
Reporting group description:	
Bivalirudin administered as a bolus and intravenous (IV) infusion. It was recommended that the bolus (0.75 milligrams per kilogram [mg/kg]) be directly administered through the valve delivery sheath immediately following its successful delivery via percutaneous femoral access. Systemic IV administration of the bolus dose was also acceptable. The bivalirudin IV infusion was initiated immediately after the bolus administration. All wires, catheters, and sheaths were to be flushed with heparinized saline.	
Reporting group title	Unfractionated heparin (UFH)
Reporting group description:	
The dose of UFH adhered to the standard institutional practice. An ACT target ≥250 seconds was recommended. All wires, catheters, and sheaths were to be flushed with heparinized saline.	

Reporting group values	Bivalirudin	Unfractionated heparin (UFH)	Total
Number of subjects	405	398	803
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)	11	10	21
From 65-84 years	230	224	454
85 years and over	164	164	328
Age continuous Units: years			
arithmetic mean	82.3	82.3	
standard deviation	± 6.5	± 6.5	-
Gender categorical Units: Subjects			
Female	195	196	391
Male	209	202	411
Not recorded	1	0	1

End points

End points reporting groups

Reporting group title	Bivalirudin

Reporting group description:

Bivalirudin administered as a bolus and intravenous (IV) infusion. It was recommended that the bolus (0.75 milligrams per kilogram [mg/kg]) be directly administered through the valve delivery sheath immediately following its successful delivery via percutaneous femoral access. Systemic IV administration of the bolus dose was also acceptable. The bivalirudin IV infusion was initiated immediately after the bolus administration. All wires, catheters, and sheaths were to be flushed with heparinized saline.

Reporting group title	Unfractionated heparin (UFH)

Reporting group description:

The dose of UFH adhered to the standard institutional practice. An ACT target ≥250 seconds was recommended. All wires, catheters, and sheaths were to be flushed with heparinized saline.

Subject analysis set title	Bivalirudin: First half of study site's enrolled participants
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This includes the first half of the site’s enrolled participants, and only sites with more than 20 participants are included in this analysis.

Subject analysis set title	Bivalirudin: Second half of study site's enrolled participants
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This includes the second half of the site’s enrolled participants, and only sites with more than 20 participants are included in this analysis.

Subject analysis set title	UFH: First half of study site's enrolled participants
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This includes the first half of the site’s enrolled participants, and only sites with more than 20 participants are included in this analysis.

Subject analysis set title	UFH: Second half of study site's enrolled participants
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This includes the second half of the site’s enrolled participants, and only sites with more than 20 participants are included in this analysis.

Primary: Major Bleeding (BARC ≥3b) at 48 hours or before hospital discharge

End point title	Major Bleeding (BARC ≥3b) at 48 hours or before hospital discharge

End point description:

Major bleeding (Bleeding Academic Research Consortium [BARC] type ≥3b) was defined as follows:

- Bleeds that were evident clinically, or by laboratory or imaging results, which resulted in surgical intervention or administration of IV vasoactive drugs; overt bleeds with a hemoglobin drop of at least 5 grams per deciliter (g/dL); and bleeding that caused cardiac tamponade.
- BARC 3c includes intracranial or intraocular bleeds that compromised vision.
- BARC type 4 (Coronary Artery Bypass Grafting [CABG]-related bleeding) includes perioperative intracranial bleeding within 48 hours, bleeds that result in reoperation following closure of sternotomy for the purpose of controlling bleeding, bleeds that result in treatment with transfusion of ≥5 units of whole blood or packed red blood cells within a 48 hour period; and chest tube output ≥ 2 L within a 24-hour period.
- BARC type 5, fatal bleeding, describes bleeds that directly result in death with no other cause.

End point type	Primary

End point timeframe:

at 48 hours or hospital discharge, whichever occurs earlier

End point values	Bivalirudin	Unfractionated heparin (UFH)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	398		
Units: Percentage of participants				
number (not applicable)	6.9	9		

Statistical analyses

Statistical analysis title	Statistical analyses
Comparison groups	Unfractionated heparin (UFH) v Bivalirudin
Number of subjects included in analysis	802
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2692
Method	Chi-squared
Parameter estimate	Relative risk
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.23

Primary: Net adverse clinical events (NACE) at up to 30 days

End point title	Net adverse clinical events (NACE) at up to 30 days

End point description:

The net adverse cardiac events (NACE) at 30 days is the composite of major adverse cardiovascular events (MACE) + major bleeding (BARC type ≥3b). The composite of MACE is defined as all-cause mortality, myocardial infarction (MI), and stroke. 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.

End point type	Primary

End point timeframe:

up to 30 days after procedure

End point values	Bivalirudin	Unfractionated heparin (UFH)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	398		
Units: Percentage of participants				
number (not applicable)	14.4	16.1		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Bivalirudin v Unfractionated heparin (UFH)
Number of subjects included in analysis	802
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4967
Method	Chi-squared
Parameter estimate	Relative risk
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.24

Secondary: NACE at 48 hours or before hospital discharge

End point title	NACE at 48 hours or before hospital discharge

End point description:

NACE at 48 hours or before hospital discharge is the composite of major adverse cardiovascular events (MACE) + major bleeding (BARC type ≥3b). The composite of MACE is defined as all-cause mortality, MI, and stroke. 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.

End point type	Secondary

End point timeframe:

at 48 hours or before hospital discharge

End point values	Bivalirudin	Unfractionated heparin (UFH)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	398		
Units: Percentage of participants				
number (not applicable)	8.9	12.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Major adverse cardiac events (MACE) including death, non-fatal MI, and stroke

End point title	Major adverse cardiac events (MACE) including death, non-fatal MI, and stroke

End point description:

The percentage of participants reporting a MACE overall and the individual components of MACE (including death, non-fatal MI, and stroke) are presented.

End point type	Secondary

End point timeframe:

at 48 hours or before hospital discharge, whichever occurred earlier, and at up to 30 days (±7 days) follow-up

End point values	Bivalirudin	Unfractionated heparin (UFH)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	398		
Units: Percentage of participants				
number (not applicable)				
MACE at 48 hours or before hospital discharge	3.5	4.8		
Death at 48 hours or before hospital discharge	1.5	1.8		
MI at 48 hours or before hospital discharge	0	1.3		
Stroke at 48 hours or before hospital discharge	2	2		
MACE at up to 30 days	7.7	8		
Death at up to 30 days	4.7	4.8		
MI at up to 30 days	0.5	1.8		
Stroke at up to 30 days	3.5	2.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Major bleeding according to additional scales (VARC, TIMI, GUSTO, ACUITY/HORIZONS);

End point title	Major bleeding according to additional scales (VARC, TIMI, GUSTO, ACUITY/HORIZONS);

End point description:

Percentage of participants wtih major bleeding according to the following scales:
Valve Academic Research Consortium (VARC)= life threatening, disabling bleeding or major bleeding
Thrombolysis in Myocardial Infarction (TIMI)=major bleeding
Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)=severe or life-threatening bleeding
Acute Catheterization and Urgent Intervention Triage StrategY (ACUITY)/ Harmonizing Outcomes with RevasculariZatiON and Stents (HORIZONS)=major bleeding

End point type	Secondary

End point timeframe:

at 48 hours or hospital discharge, whichever occurred earlier, and at up to 30 days (±7 days) follow-up

End point values	Bivalirudin	Unfractionated heparin (UFH)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	398		
Units: Percentage of participants				
number (not applicable)				
VARC at 48 hours or before hospital discharge	21.8	19.6		
TIMI at 48 hours or before hospital discharge	4	6.5		
GUSTO 48 hours or hospital discharge	3.7	3.3		
ACUITY/HORIZONS at 48 hours or hospital discharge	26	24.4		
VARC at 30 days	26.5	24.6		
TIMI at 30 days	5.7	7.3		
GUSTO at 30 days	4.2	4.3		
ACUITY/HORIZONS at 30 days	33.4	29.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Transient ischemic attack

End point title	Transient ischemic attack

End point description:

The percentage of participants reporting transient ischemic attack is presented.

End point type	Secondary

End point timeframe:

at 48 hours or before hospital discharge, whichever occurred earlier, and at up to 30 days (±7 days) follow-up

End point values	Bivalirudin	Unfractionated heparin (UFH)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	398		
Units: Percentage of participants				
number (not applicable)				
at 48 hours or before hospital discharge	0	0		
at up to 30 days (±7 days) follow-up	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Acute kidney injury

End point title	Acute kidney injury

End point description:

The percentage of participants reporting acute kidney injury is presented.

End point type	Secondary

End point timeframe:

at 48 hours or hospital discharge, whichever occurred earlier, and at up to 30 days (±7 days) follow-up

End point values	Bivalirudin	Unfractionated heparin (UFH)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	398		
Units: Percentage of participants				
number (not applicable)				
at 48 hours or before hospital discharge	10.9	6.5		
at up to 30 days (±7 days) follow-up	18.8	13.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Major vascular complications

End point title	Major vascular complications

End point description:

The percentage of patients reporting a major vascular complications as defined by VARC is presented.

End point type	Secondary

End point timeframe:

at 48 hours or before hospital discharge, whichever occurred earlier, and at up to 30 days (±7 days) follow-up

End point values	Bivalirudin	Unfractionated heparin (UFH)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	398		
Units: Percentage of participants				
number (not applicable)				
at 48 hours or before hospital discharge	8.7	9		
at up to 30 days (±7 days) follow-up	9.2	9.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Acquired thrombocytopenia

End point title	Acquired thrombocytopenia

End point description:

The percentage of participants reporting acquired thrombocytopenia is presented.

End point type	Secondary

End point timeframe:

at 48 hours or before hospital discharge, whichever occurred earlier, and at up to 30 days (±7 days) follow-up

End point values	Bivalirudin	Unfractionated heparin (UFH)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	398		
Units: Percentage of participants				
number (not applicable)				
at 48 hours or before hospital discharge	16.6	17.3		
at up to 30 days (±7 days)	24	23.1		

Statistical analyses

No statistical analyses for this end point

Secondary: New onset atrial fibrillation/flutter

End point title	New onset atrial fibrillation/flutter

End point description:

The percentage of participants reporting new onset atrial fibrillation/flutter is presented.

End point type	Secondary

End point timeframe:

at 48 hours or before hospital discharge, whichever occurred earlier, and at up to 30 days (±7 days) follow-up

End point values	Bivalirudin	Unfractionated heparin (UFH)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	398		
Units: Percentage of participants				
number (not applicable)				
at 48 hours or before hospital discharge	3.2	2.5		
at up to 30 days (±7 days) follow-up	5.4	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Economic analysis of using bivalirudin in Transcatheter-aortic valve replacement (TAVR)

End point title	Economic analysis of using bivalirudin in Transcatheter-aortic valve replacement (TAVR)

End point description:

The effect of timing on bleeding event rates (the percentage of particpants with an incidence of major bleeding) is presented.

End point type	Secondary

End point timeframe:

at hospital discharge (but also includes any subsequent hospitalizations)

End point values	Bivalirudin: First half of study site's enrolled participants	Bivalirudin: Second half of study site's enrolled participants	UFH: First half of study site's enrolled participants	UFH: Second half of study site's enrolled participants
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	173	171	173	165
Units: Percentage of participants				
number (not applicable)	6.4	6.4	11.6	8.5

Statistical analyses

No statistical analyses for this end point

Secondary: Bleeding BARC 3a, BARC types 1 or 2, and TIMI minor

End point title	Bleeding BARC 3a, BARC types 1 or 2, and TIMI minor

End point description:

The percentage of particpants with moderate bleeding as defined by BARC 3a and minor bleeding as defined as BARC type 1 & 2 and TIMI minor is presented.

End point type	Secondary

End point timeframe:

at 48 hours or hospital discharge, whichever occurred earlier, and at up to 30 days (±7 days) follow-up

End point values	Bivalirudin	Unfractionated heparin (UFH)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	398		
Units: Percentage of participants				
number (not applicable)				
BARC 3a at 48 hours or hospital discharge	15.6	13.3		
BARC types 1 and 2 at 48 hours or discharge	20.8	21.1		
TIMI minor at 48 hours or hospital discharge	16.6	14.3		
BARC 3a at 30 days	18.8	17.3		
BARC types 1 and 2 at 30 days	27.7	25.6		
TIMI minor at 30 days	21.3	19.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 30 days (± 7 days) follow up.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	Bivalirudin
Reporting group description:	
Safety population=all randomized participants who signed informed consent and received at least 1 dose of study drug	
Reporting group title	Unfractionated Heparin (UFH)
Reporting group description:	
Safety population=all randomized participants who signed informed consent and received at least 1 dose of study drug	

Serious adverse events	Bivalirudin	Unfractionated Heparin (UFH)	
Total subjects affected by serious adverse events			
subjects affected / exposed	112 / 393 (28.50%)	116 / 394 (29.44%)	
number of deaths (all causes)	19	21	
number of deaths resulting from adverse events	4	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 393 (0.00%)	2 / 394 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Hypotension			
subjects affected / exposed	2 / 393 (0.51%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 393 (0.00%)	2 / 394 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery dissection			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			

subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Intestinal anastomosis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 393 (0.25%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 1	
Device leakage			
subjects affected / exposed	1 / 393 (0.25%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	2 / 393 (0.51%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 393 (0.51%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	2 / 393 (0.51%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 393 (0.25%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Cardiac valve replacement complication			
subjects affected / exposed	3 / 393 (0.76%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac valve rupture			
subjects affected / exposed	0 / 393 (0.00%)	2 / 394 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 393 (0.00%)	2 / 394 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular procedure complication			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	46 / 393 (11.70%)	34 / 394 (8.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	7 / 393 (1.78%)	10 / 394 (2.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	6 / 393 (1.53%)	10 / 394 (2.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 3	
Bradycardia			
subjects affected / exposed	2 / 393 (0.51%)	7 / 394 (1.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 393 (0.51%)	7 / 394 (1.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 2	
Atrioventricular block second degree			
subjects affected / exposed	2 / 393 (0.51%)	6 / 394 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block first degree			
subjects affected / exposed	3 / 393 (0.76%)	4 / 394 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	2 / 393 (0.51%)	4 / 394 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	4 / 393 (1.02%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 393 (0.25%)	3 / 394 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aortic valve incompetence			

subjects affected / exposed	1 / 393 (0.25%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 393 (0.25%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiogenic shock			
subjects affected / exposed	0 / 393 (0.00%)	2 / 394 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery occlusion			
subjects affected / exposed	0 / 393 (0.00%)	2 / 394 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular fibrillation			
subjects affected / exposed	1 / 393 (0.25%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachyarrhythmia			
subjects affected / exposed	1 / 393 (0.25%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bifascicular block			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac perforation			

subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low cardiac output syndrome			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			

subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block			
subjects affected / exposed	2 / 393 (0.51%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	3 / 393 (0.76%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 3	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cognitive disorder			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhagic stroke			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Loss of consciousness			

subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 393 (0.25%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 1	
Abdominal hernia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastritis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal infarction			

subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Umbilical hernia, obstructive			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 393 (0.00%)	2 / 394 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 2	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 393 (0.51%)	2 / 394 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 393 (0.00%)	2 / 394 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 393 (0.25%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	

Bronchitis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic encephalopathy			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 393 (0.00%)	1 / 394 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 394 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Bivalirudin	Unfractionated Heparin (UFH)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 393 (18.58%)	70 / 394 (17.77%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 393 (4.83%)	16 / 394 (4.06%)	
occurrences (all)	19	16	
Cardiac disorders			
Bundle branch block left			
subjects affected / exposed	15 / 393 (3.82%)	16 / 394 (4.06%)	
occurrences (all)	15	16	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	12 / 393 (3.05%)	19 / 394 (4.82%)	
occurrences (all)	14	19	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	14 / 393 (3.56%)	10 / 394 (2.54%)	
occurrences (all)	14	10	
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all)	13 / 393 (3.31%) 13	9 / 394 (2.28%) 10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 August 2012	Amendment number 1 on 29 August 2012 included the following clinical changes to the protocol: • Clarification of secondary endpoints. Valve performance indicators and TAVR-specific complications and rate of persistent, profound hypotension were deleted. • Correction on listed document for information on potential risks of bivalirudin. • Inclusion of patients with severe renal impairment was specified on request of regulatory authorities; only dialysis-dependent patients were excluded. • Clarification of 30 days patient management following PCI irrespective of drug-eluting stents (DES) or bare-metal stents (BMS). • The following examinations had only to be done once if screening and randomisation were close together (≤48 hrs): medical history, medical examination, neurological assessment (Rankin score), blood hematology, blood chemistry. • Dose justification for bivalirudin was added at the request of regulatory authorities • Neurological examination for the study population was specified. Detailed neurological assessment (only for the magnetic resonance imaging [MRI]-substudy) has been clarified. • LVEF to be done only at screening. • International normalized ratio (INR) to be done only at randomization. • Pregnancy test added at the request of regulatory authorities. • Any ECG source can be used for the ECG examination: 12-lead ECG examination changed to ECG. • Changes to enrollment and pre-procedure management • Arterial site and sheath size were deleted. • Management of bleeding while on treatment with bivalirudin added on request of regulatory authority. • Examinations for follow-up visit were updated. • Scheduled corrected to include AE-recording up to hospital discharge. • Observational period up to day 30 specified. • Pre-TAVR-MRI not needed for MRI-substudy. • In addition, several administrative changes were made and typos were fixed.

12 February 2014	Amendment number 2 on 12 February 2014 included the following clinical changes to the protocol: • Change to the primary endpoint. The definition of the primary study endpoint of major bleeding changed to BARC type ≥ 3b (from BARC type ≥ 3). • Change to the secondary endpoints related to and consistent with the change to the primary endpoint. • Text describing BARC bleeding by type revised for consistency with the current primary and secondary endpoint designations and for completeness. • Clarification to procedures for 30-day follow-up to specify that in the event of phone follow-up for study patients, data collection was with the health care professional. • Clarification to procedures for study drug administration to specify flushing with heparinized saline, in line with best practices and supportive documentation. • Clarification to procedure for bivalirudin vial reconstitution to most accurately convey time that may be needed for dissolution. • Change to BRAVO MRI Substudy neurological assessments to designate National Institutes of Health Stroke Scale (NIHSS) and Mini-Mental State Examination (MMSE) as optional. • Clarification to BRAVO Economic Substudy text with more precise wording and additional description. • In addition, several administrative changes were made and typos were fixed.
30 August 2014	Amendment number 3 on 30 August 2014 complied with a recommendation from the Data and Safety Monitoring Board (DSMB) to increase the sample size of the trial based on DSMB review of the second interim analysis of the trial according to prespecified statistical methods. The BRAVO 2/3 study sample size was designed to achieve 80% power and was based on estimated bleeding rate. The trial was also designed to include a second interim analysis after the enrolment of 340 randomised patients (approximately 2/3 of the projected study enrolment). The second interim analysis was an unblinded determination of major bleeding rates in each BRAVO 2/3 treatment group, observed relative risk reduction, and conditional power based on assumed sample sizes. The DSMB reviewed summary reports of the second interim analysis and the adaptive sample size calculations prepared by independent statisticians and convened on 22 May 2014 to determine their recommendation. On 23 May 2014, the DSMB issued a recommendation to continue the trial unmodified until the final number of randomized patients reached the upper limit of 800 patients defined in the interim statistical analysis plan. Accordingly, the following changes were made to the protocol: • Change to the total number of patients to be included in the trial, from 620 to 870. • Change to the number of randomized patients to be included in the trial, from 550 to 800. • A description of DSMB review of the second interim analysis results and addition of the consequent DSMB recommendation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported