Clinical trial results:
A Single-blinded, Randomized, Controlled, Comparative Phase III Study Evaluating the Safety and Effectiveness of EVARREST™ Fibrin Sealant Patch
as an Adjunct to Hemostasis During Cardiovascular Surgery

Summary

EudraCT number	2013-003464-31
Trial protocol	GB BE
Global end of trial date	23 September 2015

Results information

Result version number	v1 (current)
This version publication date	16 July 2017
First version publication date	16 July 2017

Trial information

Trial identification

Sponsor protocol code	BIOS-13-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02040428
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ETHICON , a Johnson & Johnson Company
Sponsor organisation address	Route 22 West , Somerville, United States, NJ 08876-0151
Public contact	Dr Leonie Rynn, Clinical Development, ETHICON, a Johnson & Johnson Company., 001 908-218-2492, lrynn1@its.jnj.com
Scientific contact	Dr Richard Kocharian, Medical Director , ETHICON, a Johnson & Johnson Company., 001 908-218-2013, rkochar1@ITS.JNJ.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	02 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2015
Global end of trial reached?	Yes
Global end of trial date	23 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to evaluate the safety and effectiveness of the EVARREST™ Fibrin Sealant Patch as an adjunct to hemostasis during cardiovascular surgery.

Protection of trial subjects:

The protocol and consent form were provided to the appriopriate Ethics Committee for approval . In adddition, an independant Data Monitoring Committee was established and had responsibility for evaluating the progress of the trial and assessing patient safety and data quality.

Background therapy:

Not applicable

Evidence for comparator:

TachoSil® Absorbable Fibrin Sealant Patch was used as the comparator and was applied according to it's approved label and instructions for use (IFU).

Actual start date of recruitment	13 January 2014
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	United Kingdom: 34
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	United States: 62
Country: Number of subjects enrolled	Australia: 33
Country: Number of subjects enrolled	Japan: 20
Worldwide total number of subjects	156
EEA total number of subjects	41

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)	79
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was recruited on the 13 January 2014 and the last patient completed 23 September 2015.

Pre-assignment

Screening details:

Prospective patients were screened within 21 days prior to surgery. Prior to any study specific procedures, subjects were fully informed of all aspects of the study and asked to sign a consent form. In Japan, subjects ≥18 and <20 required to have their consent signed by the subject's legal representative.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Actual treatment not discussed with the patient.

Arms

Are arms mutually exclusive?	Yes
Arm title	EVARREST™ Fibrin Sealant Patch

Arm description:

Investigational Product

Arm type	Experimental
Investigational medicinal product name	EVARREST™ Fibrin Sealant Patch
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sealant matrix
Routes of administration	Topical use

Dosage and administration details:

After identification of the TBS, EVARREST was to be trimmed to an appropriate size to cover the TBS, allowing sufficient overlap (1 to 2 cm) onto non-bleeding areas, and then placed over the TBS. After correct application had been verified, firm manual compression sufficient to stem all bleeding at the TBS was to be maintained for 3 minutes per the instructions for use. The surgeon could use a surgical sponge to assist in providing adequate pressure over the entire surface of the EVARREST patch.

No more than four units (10.2 x 10.2 cm / 4 x 4 inches) of EVARREST were to be left implanted in subjects treated with EVARREST.

Arm title	TachoSil®

Arm description:

Comparator product

Arm type	Active Comparator

No investigational medicinal product assigned in this arm

Number of subjects in period 1	EVARREST™ Fibrin Sealant Patch	TachoSil®
Started	75	81
Completed	70	77
Not completed	5	4
Adverse event, serious fatal	4	3
Consent withdrawn by subject	1	1

Baseline characteristics

Reporting groups	
Reporting group title	EVARREST™ Fibrin Sealant Patch
Reporting group description: Investigational Product	
Reporting group title	TachoSil®
Reporting group description: Comparator product	

Reporting group values	EVARREST™ Fibrin Sealant Patch	TachoSil®	Total
Number of subjects	75	81	156
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)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults (18-<50 years)	14	12	26
Adults (50-<65 years)	21	32	53
Adults (65-<75 years)	22	25	47
Adults (>=75 years)	18	12	30
Gender categorical Units: Subjects			
Female	19	20	39
Male	56	61	117

End points

End points reporting groups

Reporting group title	EVARREST™ Fibrin Sealant Patch
Reporting group description: Investigational Product	
Reporting group title	TachoSil®
Reporting group description: Comparator product	
Subject analysis set title	Intent to Treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intent-to- treat set (ITT or full analysis set) consisting of all randomized subjects. Subjects who did not complete the procedure after randomization were to be considered as failures and included in the ITT analysis.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: Safety set consisting of all subjects on whom the study procedure was started.	
Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description: All subjects in the ITT analysis set who had no major protocol violations.	

Primary: Hemostasis at the TBS at 3 minutes and maintence to chest wall closure.

End point title	Hemostasis at the TBS at 3 minutes and maintence to chest wall closure.
End point description: Hemostasis at the TBS at 3 minutes following treatment application and with no rebleeding requiring treatment at the TBS any time prior to initiation of final chest wall closure. Hemostasis is defined as no detectable bleeding at the TBS.	
End point type	Primary
End point timeframe: Up to final chest wall closure	

End point values	EVARREST™ Fibrin Sealant Patch	TachoSil®	Intent to Treat	Per Protocol
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	75[1]	81[2]	156	141
Units: Percentage of successes	76	80	156	141

Notes:

[1] - 31107 randomized to EVARREST received TachoSil, analysed in EVARREST ITT & in Tachosil for Safety

[2] - 31107 randomized to EVARREST received TachoSil, analysed in EVARREST ITT & in Tachosil for Safety

Statistical analyses

Statistical analysis title	Primary Efficacy Endpoint
Comparison groups	EVARREST™ Fibrin Sealant Patch v TachoSil®

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Chi-squared

Secondary: Hemostasis at the TBS at 6 minutes and maintence to final chest wall closure.

End point title	Hemostasis at the TBS at 6 minutes and maintence to final chest wall closure.

End point description:

Hemostasis at the TBS at 6 minutes following treatment application and with no rebleeding requiring treatment at the TBS any time prior to initiation of final chest wall closure.

End point type	Secondary

End point timeframe:

Hemostasis at the TBS at 6 minutes and maintence to final chest wall closure.

End point values	EVARREST™ Fibrin Sealant Patch	TachoSil®	Intent to Treat	Per Protocol
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	75[3]	81[4]	156[5]	141
Units: Percentage of successes	76	80	156	141

Notes:

[3] - 31107 randomized to EVARREST received TachoSil, analysed in EVARREST ITT & in Tachosil for Safety

[4] - 31107 randomized to EVARREST received TachoSil, analysed in EVARREST ITT & in Tachosil for Safety

[5] - Subject 31107 was randomized to EVARREST and received TachoSil, subject was analysed in EVARREST

Statistical analyses

Statistical analysis title	Secondary Endpoint Analysis
Comparison groups	EVARREST™ Fibrin Sealant Patch v TachoSil®
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0046
Method	logistics model
Parameter estimate	Log odds ratio
Confidence interval	
level	95 %
sides	2-sided

Secondary: Hemostasis at the TBS at 10 minutes and maintence to final chest wall closure.

End point title	Hemostasis at the TBS at 10 minutes and maintence to final chest wall closure.

End point description:

Hemostasis at the TBS at 10 minutes following treatment application and with no rebleeding requiring treatment at the TBS any time prior to initiation of final chest wall closure.

End point type	Secondary

End point timeframe:

Hemostasis at the TBS at 10 minutes and maintence to final chest wall closure

End point values	EVARREST™ Fibrin Sealant Patch	TachoSil®	Intent to Treat	Per Protocol
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	75[6]	81[7]	156	141
Units: Percentage of successes	76	80	156	141

Notes:

[6] - 31107 randomized to EVARREST received TachoSil, analysed in EVARREST ITT & in Tachosil for Safety

[7] - 31107 randomized to EVARREST received TachoSil, analysed in EVARREST ITT & in Tachosil for Safety

Statistical analyses

Statistical analysis title	Secondary Endpoint Analysis
Comparison groups	EVARREST™ Fibrin Sealant Patch v TachoSil®
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0352
Method	logistics model
Parameter estimate	Log odds ratio
Confidence interval	
level	95 %
sides	2-sided

Secondary: Incidence of rebleeding requiring treatment after initial establishment of TBS hemostasis at 3 minutes.

End point title	Incidence of rebleeding requiring treatment after initial establishment of TBS hemostasis at 3 minutes.

End point description:

Incidence of rebleeding requiring treatment after initial establishment of TBS hemostasis at 3 minutes.

End point type	Secondary

End point timeframe:

Incidence of rebleeding requiring treatment after initial establishment of TBS hemostasis at 3 minutes.

End point values	EVARREST™ Fibrin Sealant Patch	TachoSil®	Intent to Treat	Per Protocol
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	75[8]	81[9]	156	141
Units: Percentage of successes	76	80	156	141

Notes:

[8] - 31107 randomized to EVARREST received TachoSil, analysed in EVARREST ITT & in Tachosil for Safety

[9] - 31107 randomized to EVARREST received TachoSil, analysed in EVARREST ITT & in Tachosil for Safety

Statistical analyses

Statistical analysis title	Secondary Endpoint Analysis
Comparison groups	EVARREST™ Fibrin Sealant Patch v TachoSil®
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0046 [10]
Method	Chi-squared
Confidence interval	
sides	2-sided

Notes:

[10] - P-value noted above is for Haemostatic success at 6 mins

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events (collected from time of randomization, throughout the follow-up period until approximately 60-days after the procedure)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15

Reporting groups	
Reporting group title	EVARREST™ Fibrin Sealant Patch
Reporting group description: -	
Reporting group title	TachoSil® Fibrin Sealant Patch
Reporting group description:	
TachoSil® Fibrin Sealant Patch	

Serious adverse events	EVARREST™ Fibrin Sealant Patch	TachoSil® Fibrin Sealant Patch	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 75 (41.33%)	34 / 81 (41.98%)	
number of deaths (all causes)	4	3	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ Failure			
subjects affected / exposed	2 / 75 (2.67%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	6 / 75 (8.00%)	7 / 81 (8.64%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumothorax			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 75 (4.00%)	3 / 81 (3.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Anticoagulation drug level above therapeutic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio fluctuation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
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			
Anastomotic haemorrhage			
subjects affected / exposed	4 / 75 (5.33%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial injury			

subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac procedure complication			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	3 / 75 (4.00%)	3 / 81 (3.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative thoracic procedure complication			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial depression			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			

subjects affected / exposed	7 / 75 (9.33%)	8 / 81 (9.88%)	
occurrences causally related to treatment / all	0 / 7	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	2 / 75 (2.67%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	3 / 75 (4.00%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 75 (1.33%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	3 / 75 (4.00%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 75 (1.33%)	3 / 81 (3.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			

subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain injury			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 75 (1.33%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
convulsion			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	2 / 75 (2.67%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 75 (1.33%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			

subjects affected / exposed	1 / 75 (1.33%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
bronchopneumonia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 75 (2.67%)	3 / 81 (3.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Postoperative wound infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (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: 5 %

Non-serious adverse events	EVARREST™ Fibrin Sealant Patch	TachoSil® Fibrin Sealant Patch	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 75 (97.33%)	80 / 81 (98.77%)	
Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	

Blood pressure fluctuation			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Deep vein thrombosis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	2	
Haematoma			
subjects affected / exposed	2 / 75 (2.67%)	4 / 81 (4.94%)	
occurrences (all)	2	4	
Haemodynamic instability			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	4 / 75 (5.33%)	9 / 81 (11.11%)	
occurrences (all)	5	9	
Hypotension			
subjects affected / exposed	15 / 75 (20.00%)	18 / 81 (22.22%)	
occurrences (all)	15	18	
Iliac artery occlusion			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Peripheral coldness			
subjects affected / exposed	1 / 75 (1.33%)	2 / 81 (2.47%)	
occurrences (all)	1	2	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Vasodilatation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Venous thrombosis limb			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	

Surgical and medical procedures			
Thoracic cavity drainage			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Catheter site inflammation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Catheter site pain			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Catheter site related reaction			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	5 / 75 (6.67%)	3 / 81 (3.70%)	
occurrences (all)	8	3	
Chills			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Crepitations			
subjects affected / exposed	1 / 75 (1.33%)	2 / 81 (2.47%)	
occurrences (all)	1	2	
Extravasation			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Gait disturbance			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Generalised oedema			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Hypothermia			

subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Implant site extravasation			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
medical device complication			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Multi-organ failure			
subjects affected / exposed	2 / 75 (2.67%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Oedema			
subjects affected / exposed	1 / 75 (1.33%)	4 / 81 (4.94%)	
occurrences (all)	1	4	
Oedema peripheral			
subjects affected / exposed	5 / 75 (6.67%)	13 / 81 (16.05%)	
occurrences (all)	5	14	
Pain			
subjects affected / exposed	9 / 75 (12.00%)	11 / 81 (13.58%)	
occurrences (all)	11	13	
Pyrexia			
subjects affected / exposed	11 / 75 (14.67%)	10 / 81 (12.35%)	
occurrences (all)	13	11	
Secretion discharge			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Tenderness			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	2	

Thirst			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Scrotal swelling			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Acute lung injury			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Acute pulmonary oedema			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Acute respiratory failure			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Atelectasis			
subjects affected / exposed	6 / 75 (8.00%)	12 / 81 (14.81%)	
occurrences (all)	6	13	
Bronchospasm			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Cough			

subjects affected / exposed	4 / 75 (5.33%)	6 / 81 (7.41%)	
occurrences (all)	4	6	
Dysphonia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	7 / 75 (9.33%)	5 / 81 (6.17%)	
occurrences (all)	7	5	
Epistaxis			
subjects affected / exposed	1 / 75 (1.33%)	2 / 81 (2.47%)	
occurrences (all)	1	2	
Haemothorax			
subjects affected / exposed	0 / 75 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
Hypoxia			
subjects affected / exposed	2 / 75 (2.67%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Lung infiltration			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	24 / 75 (32.00%)	22 / 81 (27.16%)	
occurrences (all)	29	22	
Pneumonia aspiration			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Pneumothorax			
subjects affected / exposed	8 / 75 (10.67%)	5 / 81 (6.17%)	
occurrences (all)	8	5	
Pulmonary congestion			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Pulmonary embolism			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Pulmonary haemorrhage			

subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Pulmonary hypertension			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Pulmonary oedema			
subjects affected / exposed	5 / 75 (6.67%)	4 / 81 (4.94%)	
occurrences (all)	5	4	
Respiratory failure			
subjects affected / exposed	3 / 75 (4.00%)	3 / 81 (3.70%)	
occurrences (all)	4	3	
Wheezing			
subjects affected / exposed	2 / 75 (2.67%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Anxiety			
subjects affected / exposed	2 / 75 (2.67%)	5 / 81 (6.17%)	
occurrences (all)	2	5	
Confusional state			
subjects affected / exposed	3 / 75 (4.00%)	6 / 81 (7.41%)	
occurrences (all)	3	6	
Delirium			
subjects affected / exposed	3 / 75 (4.00%)	7 / 81 (8.64%)	
occurrences (all)	3	7	
Depression			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Hallucination			
subjects affected / exposed	3 / 75 (4.00%)	0 / 81 (0.00%)	
occurrences (all)	3	0	
Insomnia			
subjects affected / exposed	1 / 75 (1.33%)	9 / 81 (11.11%)	
occurrences (all)	1	9	

Panic attack			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Paranoia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Psychiatric symptom			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Restlessness			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Stress			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Disorientation			
subjects affected / exposed	2 / 75 (2.67%)	2 / 81 (2.47%)	
occurrences (all)	2	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Anticoagulation drug level above therapeutic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Blood creatine increased			
subjects affected / exposed	2 / 75 (2.67%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Blood electrolytes decreased			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Blood fibrinogen increased			

subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Blood glucose fluctuation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Blood lactic acid decreased			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Blood lactic acid increased			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Breath sounds abnormal			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	2 / 75 (2.67%)	2 / 81 (2.47%)	
occurrences (all)	2	2	
Cardiac murmur			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Cardiac output decreased			
subjects affected / exposed	2 / 75 (2.67%)	1 / 81 (1.23%)	
occurrences (all)	3	1	
Central venous pressure decreased			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Chest X-ray abnormal			
subjects affected / exposed	0 / 75 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
Electrocardiogram ST segment elevation			
subjects affected / exposed	1 / 75 (1.33%)	2 / 81 (2.47%)	
occurrences (all)	1	2	
Enterococcus test positive			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	

Haematocrit decreased			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Heart rate decreased			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Heart rate increased			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Heart rate irregular			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Inspiratory capacity decreased			
subjects affected / exposed	2 / 75 (2.67%)	3 / 81 (3.70%)	
occurrences (all)	2	3	
International normalised ratio fluctuation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
International normalised ratio increased			
subjects affected / exposed	0 / 75 (0.00%)	3 / 81 (3.70%)	
occurrences (all)	0	3	
Klebsiella test positive			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Liver function test abnormal			
subjects affected / exposed	2 / 75 (2.67%)	4 / 81 (4.94%)	
occurrences (all)	2	4	
Neurological examination abnormal			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Oxygen saturation decreased			
subjects affected / exposed	3 / 75 (4.00%)	1 / 81 (1.23%)	
occurrences (all)	3	1	
Prothrombin time prolonged			

subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Staphylococcus test positive			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Thoracic cavity drainage test abnormal			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Urine output decreased			
subjects affected / exposed	3 / 75 (4.00%)	4 / 81 (4.94%)	
occurrences (all)	3	4	
Weight decreased			
subjects affected / exposed	2 / 75 (2.67%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Weight increased			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	2 / 75 (2.67%)	3 / 81 (3.70%)	
occurrences (all)	2	3	
Anastomotic haemorrhage			
subjects affected / exposed	4 / 75 (5.33%)	1 / 81 (1.23%)	
occurrences (all)	4	1	
Arterial injury			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Cardiac procedure complication			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Contusion			

subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)		
occurrences (all)	1	1		
Donor site complication				
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)		
occurrences (all)	0	1		
Excoriation				
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)		
occurrences (all)	1	0		
Head injury				
subjects affected / exposed	2 / 75 (2.67%)	1 / 81 (1.23%)		
occurrences (all)	2	1		
Injury corneal				
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)		
occurrences (all)	1	0		
Laceration				
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)		
occurrences (all)	0	1		
Limb injury				
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)		
occurrences (all)	1	0		
Mouth injury				
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)		
occurrences (all)	0	1		
Muscle strain				
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)		
occurrences (all)	1	0		
Post procedural haemorrhage				
subjects affected / exposed	5 / 75 (6.67%)	4 / 81 (4.94%)		
occurrences (all)	6	4		
Post procedural persistant drain fluid				
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)		
occurrences (all)	1	0		
Postoperative thoracic procedure complication				
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)		
occurrences (all)	1	0		

Procedural complication			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Procedural dizziness			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	9 / 75 (12.00%)	5 / 81 (6.17%)	
occurrences (all)	11	7	
Seroma			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Subdural haemorrhage			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Suture related complication			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Venous injury			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Wound complication			
subjects affected / exposed	3 / 75 (4.00%)	9 / 81 (11.11%)	
occurrences (all)	3	9	
Wound dehiscence			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Wound secretion			
subjects affected / exposed	3 / 75 (4.00%)	3 / 81 (3.70%)	
occurrences (all)	3	3	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Arrhythmia			

subjects affected / exposed	2 / 75 (2.67%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Arrhythmia supraventricular			
subjects affected / exposed	0 / 75 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
Atrial fibrillation			
subjects affected / exposed	34 / 75 (45.33%)	29 / 81 (35.80%)	
occurrences (all)	35	32	
Atrial flutter			
subjects affected / exposed	2 / 75 (2.67%)	2 / 81 (2.47%)	
occurrences (all)	2	2	
Atrioventricular block			
subjects affected / exposed	2 / 75 (2.67%)	1 / 81 (1.23%)	
occurrences (all)	4	1	
Atrioventricular block complete			
subjects affected / exposed	2 / 75 (2.67%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Atrioventricular block first degree			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Bradycardia			
subjects affected / exposed	2 / 75 (2.67%)	2 / 81 (2.47%)	
occurrences (all)	2	2	
Bundle branch block left			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Cardiac arrest			
subjects affected / exposed	2 / 75 (2.67%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Cardiac failure			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Cardiac failure congestive			
subjects affected / exposed	4 / 75 (5.33%)	1 / 81 (1.23%)	
occurrences (all)	4	1	
Cardiac tamponade			

subjects affected / exposed	1 / 75 (1.33%)	2 / 81 (2.47%)		
occurrences (all)	1	2		
Cardiogenic shock				
subjects affected / exposed	3 / 75 (4.00%)	0 / 81 (0.00%)		
occurrences (all)	3	0		
Extrasystoles				
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)		
occurrences (all)	1	1		
Myocardial depression				
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)		
occurrences (all)	0	1		
Nodal rhythm				
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)		
occurrences (all)	1	0		
Palpitations				
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)		
occurrences (all)	1	0		
Pericardial effusion				
subjects affected / exposed	1 / 75 (1.33%)	8 / 81 (9.88%)		
occurrences (all)	1	8		
Pericarditis				
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)		
occurrences (all)	0	1		
Postural orthostatic tachycardia syndrome				
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)		
occurrences (all)	1	0		
Right ventricular failure				
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)		
occurrences (all)	1	0		
Sinus bradycardia				
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)		
occurrences (all)	0	1		
Supraventricular extrasystoles				
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)		
occurrences (all)	1	1		

Tachyarrhythmia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	3 / 75 (4.00%)	5 / 81 (6.17%)	
occurrences (all)	3	5	
Trifascicular block			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Ventricular extrasystoles			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Ventricular fibrillation			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Ventricular tachycardia			
subjects affected / exposed	3 / 75 (4.00%)	1 / 81 (1.23%)	
occurrences (all)	3	1	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Brain injury			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Cerebrovascular accident			
subjects affected / exposed	1 / 75 (1.33%)	2 / 81 (2.47%)	
occurrences (all)	1	2	
convulsion			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Cubital tunnel syndrome			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Dementia			

subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	5 / 75 (6.67%)	3 / 81 (3.70%)	
occurrences (all)	5	3	
encephalopathy			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Epilepsy			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Grand Mal convulsion			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	2 / 75 (2.67%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Hemiparesis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Hypoaesthesia			
subjects affected / exposed	0 / 75 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Lethargy			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Loss of consciousness			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Neuralgia			

subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Neuropathy peripheral			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	2	
Presyncope			
subjects affected / exposed	2 / 75 (2.67%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Somnolence			
subjects affected / exposed	1 / 75 (1.33%)	2 / 81 (2.47%)	
occurrences (all)	1	2	
Syncope			
subjects affected / exposed	0 / 75 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
Tremor			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Vocal cord paralysis			
subjects affected / exposed	0 / 75 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 75 (24.00%)	21 / 81 (25.93%)	
occurrences (all)	18	22	
Coagulopathy			
subjects affected / exposed	3 / 75 (4.00%)	4 / 81 (4.94%)	
occurrences (all)	3	4	
Haemolytic anaemia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Haemorrhagic anaemia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	

Leukocytosis			
subjects affected / exposed	2 / 75 (2.67%)	4 / 81 (4.94%)	
occurrences (all)	2	4	
Lymphopenia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	7 / 75 (9.33%)	7 / 81 (8.64%)	
occurrences (all)	7	7	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Meniere's disease			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Eye pain			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Miosis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	2 / 75 (2.67%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Visual impairment			
subjects affected / exposed	2 / 75 (2.67%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Abdominal pain			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Abdominal wall haematoma			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	15 / 75 (20.00%)	15 / 81 (18.52%)	
occurrences (all)	17	18	
Diarrhoea			
subjects affected / exposed	8 / 75 (10.67%)	2 / 81 (2.47%)	
occurrences (all)	9	2	
Dyspepsia			
subjects affected / exposed	1 / 75 (1.33%)	2 / 81 (2.47%)	
occurrences (all)	1	2	
Dysphagia			
subjects affected / exposed	0 / 75 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 75 (2.67%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 75 (2.67%)	4 / 81 (4.94%)	
occurrences (all)	2	4	
Haematemesis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Haematochezia			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Haemorrhoids			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	

Ileus			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Intestinal ischaemia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Loose tooth			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Mouth haemorrhage			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	19 / 75 (25.33%)	20 / 81 (24.69%)	
occurrences (all)	24	23	
Oral mucosal erythema			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Stomatitis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Tongue discolouration			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Tongue oedema			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	5 / 75 (6.67%)	7 / 81 (8.64%)	
occurrences (all)	5	8	
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Cholelithiasis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Hepatitis acute			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Ischaemic hepatitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Jaundice			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Decubitus ulcer			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Erythema			
subjects affected / exposed	2 / 75 (2.67%)	2 / 81 (2.47%)	
occurrences (all)	2	2	
Night sweats			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Pruritus			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	

Skin exfoliation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Subcutaneous emphysema			
subjects affected / exposed	3 / 75 (4.00%)	1 / 81 (1.23%)	
occurrences (all)	3	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 75 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
Haemorrhage urinary tract			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Renal Failure			
subjects affected / exposed	2 / 75 (2.67%)	3 / 81 (3.70%)	
occurrences (all)	2	3	
Renal failure acute			
subjects affected / exposed	3 / 75 (4.00%)	5 / 81 (6.17%)	
occurrences (all)	4	5	
Renal impairment			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Urinary retention			
subjects affected / exposed	1 / 75 (1.33%)	2 / 81 (2.47%)	
occurrences (all)	1	2	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Hypothyroidism			

subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Back pain			
subjects affected / exposed	1 / 75 (1.33%)	2 / 81 (2.47%)	
occurrences (all)	1	2	
Joint stiffness			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Limb discomfort			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	2 / 75 (2.67%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
aspergillosis			

subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Bacteraemia			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
bronchopneumonia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
candidiasis			
subjects affected / exposed	2 / 75 (2.67%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Cellulitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Cystitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Escherichia infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Fungal skin infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis viral			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Graft infection			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Haemophilus infection			
subjects affected / exposed	2 / 75 (2.67%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 75 (2.67%)	3 / 81 (3.70%)	
occurrences (all)	2	3	
Nasopharyngitis			

subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	5 / 75 (6.67%)	4 / 81 (4.94%)	
occurrences (all)	5	4	
Postoperative wound infection			
subjects affected / exposed	1 / 75 (1.33%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Respiratory tract infection			
subjects affected / exposed	3 / 75 (4.00%)	3 / 81 (3.70%)	
occurrences (all)	3	3	
Sepsis			
subjects affected / exposed	3 / 75 (4.00%)	1 / 81 (1.23%)	
occurrences (all)	3	1	
Sputum purulent			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Staphylococcal infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
tooth abcess			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 75 (2.67%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	9 / 75 (12.00%)	5 / 81 (6.17%)	
occurrences (all)	9	5	
wound infection			
subjects affected / exposed	4 / 75 (5.33%)	4 / 81 (4.94%)	
occurrences (all)	4	5	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	2 / 75 (2.67%)	0 / 81 (0.00%)	
occurrences (all)	2	0	

Decreased appetite			
subjects affected / exposed	2 / 75 (2.67%)	2 / 81 (2.47%)	
occurrences (all)	2	2	
Dehydration			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Electrolyte imbalance			
subjects affected / exposed	2 / 75 (2.67%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Fluid imbalance			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Fluid overload			
subjects affected / exposed	12 / 75 (16.00%)	11 / 81 (13.58%)	
occurrences (all)	13	12	
Fluid retention			
subjects affected / exposed	2 / 75 (2.67%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Gout			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	11 / 75 (14.67%)	11 / 81 (13.58%)	
occurrences (all)	11	11	
Hyperkalaemia			
subjects affected / exposed	6 / 75 (8.00%)	2 / 81 (2.47%)	
occurrences (all)	7	2	
Hypermagnesaemia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Hypernatraemia			
subjects affected / exposed	3 / 75 (4.00%)	0 / 81 (0.00%)	
occurrences (all)	3	0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 75 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	

Hypocalcaemia			
subjects affected / exposed	6 / 75 (8.00%)	4 / 81 (4.94%)	
occurrences (all)	6	4	
Hypoglycaemia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	7 / 75 (9.33%)	7 / 81 (8.64%)	
occurrences (all)	8	8	
Hypomagnesaemia			
subjects affected / exposed	3 / 75 (4.00%)	5 / 81 (6.17%)	
occurrences (all)	3	5	
Hyponatraemia			
subjects affected / exposed	5 / 75 (6.67%)	1 / 81 (1.23%)	
occurrences (all)	5	1	
Hypophosphataemia			
subjects affected / exposed	6 / 75 (8.00%)	3 / 81 (3.70%)	
occurrences (all)	6	3	
Hypovolaemia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Malnutrition			
subjects affected / exposed	0 / 75 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
Metabolic acidosis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Metabolic alkalosis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 81 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2013	Amendment 1 modified the stopping rule relating to treatment-related post-operative bleeding at the TBS, to clarify that this was only to apply to subjects in the EVARREST treatment group. This amendment was made before the start of subject recruitment.
18 August 2014	Amendment 2 deleted a stopping rule that had been included in the phase 2 protocol 400-12-002 but was not appropriate for the phase 3 study. The rule stated that the study should be stopped if three subjects in the EVARREST treatment arm had an intra-operative TBS re-bleeding event after 10 minutes post-application and prior to final chest wall closure that required re-intervention. The Phase 3 study design assumes 80% of EVARREST subjects will be successful; thus the failure rate assumed in the study is well above the three occurrence outlined in this stopping rule. This stopping rule was invoked on one occasion prior to implementation of Amendment 2.
19 January 2015	The principal change in amendment 3 was the clarification that the TBS could be identified during any reperfusion of the arterial anastomoses and not just the first. In addition the Amendment 3 allowed heparin reversal and removal from cardiopulmonary bypass any time after product application as well as clarifying retreatment due to product failure. Names and roles of study personnel were also updated and a number of clarifications made to protocol wording.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
21 August 2014	On 21 August 2014 one of the stopping rules was met due to a subject 16101 developing post-operative bleeding at the Target Bleeding Site (TBS) in the EVARREST treatment arm as per protocol administrative change 1, dated 22Jan2014. This stopping rule triggered a temporary halt of the trial in all study regions (United States, Australia, Japan, and EU). The DMC met on 05 September 2014 to review this specific event as well as overall safety data for the trial. The DMC recommendation was to continue the trial unmodified and the temporary enrollment halt was lifted on 08 September 2014.	08 September 2014

18 November 2014	On 18 November 2014 one of the stopping rules was met The stopping rule met was the following: three subjects in the EVARREST treatment arm had an intraoperative TBS re bleeding event after 10 minutes postapplication and prior to final chest wall closure that required reintervention. The US was the only study region impacted by this temporary halt because this stopping rule was predefined in the protocol administrative change 1, dated 22Jan2014. The other study regions - EU, Australia and Japan - were not impacted by this stopping rule since these regions were approved to conduct the study as per Protocol Amendment 2, dated 18 August 2014. This stopping rule was removed from protocol amendment 2, dated 18 August 2014 (see Section 9.8). The DMC met on 24 November 2014 to review three intra-operative TBS re-bleeding events. The DMC recommendation for the second temporary halt was to continue the trial unmodified and the temporary halt was lifted on 28 November 2014 in the US.	28 November 2014
09 December 2014	On 09 December 2014 the third temporary study halt was due to a subject in the EVARREST treatment arm developing post-operative bleeding at the (TBS) as per the stopping rule in protocol Amendment 2, dated 18 August 2014. All study regions were impacted by this temporary halt in order for the DMC to assess the event of Anastomotic Hemorrhage (Subject 31109) and overall safety data for the study. The DMC met on 23 December 2014 and 02 January 2015. The third temporary halt was lifted on 08 January 2015. The DMC also agreed with the Sponsor’s proposal to proceed with training and technical support provided to new product users. The protocol was also amended (Amendment 3, 19 January 2015) to allow heparin reversal and removal from cardiopulmonary bypass any time after product application as well as clarifying retreatment due to product failure.	08 January 2015

Notes:

Limitations and caveats

None reported