Clinical trial results:
Single centre randomised controlled trial to assess the effect of the addition of twenty-four hours of oral tranexamic acid post-operatively to a single intra-operative intravenous dose of tranexamic acid on calculated blood loss following primary hip and knee arthroplasty.

Summary

EudraCT number	2015-002661-36
Trial protocol	GB
Global end of trial date	08 July 2019

Results information

Result version number	v1 (current)
This version publication date	19 December 2020
First version publication date	19 December 2020

Trial information

Trial identification

Sponsor protocol code	15039DB-SW

Additional study identifiers

ISRCTN number	ISRCTN58790500
ClinicalTrials.gov id (NCT number)	NCT03690037
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Belfast Health and Social Care Trust (BHSCT)
Sponsor organisation address	The Royal Hospitals Grosvenor Road, Belfast, United Kingdom, BT12 6BN
Public contact	Janet Hill, Primary Joint Unit, Musgrave Park Hospital, +44 028 9504 1753, Janet.Hill@belfasttrust.hscni.net
Scientific contact	Professor David Beverland, Primary Joint Unit, Musgrave Park Hospital, +44 07736679869 , david.beverland@belfasttrust.hscni.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 July 2018
Global end of trial reached?	Yes
Global end of trial date	08 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine if the use of oral tranexamic acid post-operatively for up to 24 hours will confer a reduction in calculated blood loss at 48 hours beyond an intra-operative intravenous bolus alone for patients undergoing unilateral primary total hip or knee replacement.

Protection of trial subjects:

This study investigated the efficacy in using tranexamic acid (TXA) in primary hip and knee arthroplasty and did not subject the patient to any unnecessary risk, pain or discomfort. A risk assessment was carried out by Sponsor prior to trial initiation and a comprehensive exclusion criteria was put in place while patients were also monitored for renal impairment before being prescribed the study drug. An independent Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC) were also convened to monitor and guide overall progress while protecting the rights and safety of trial patients.

Background therapy:

All the intervention groups will have primary hip or knee arthroplasty.

Evidence for comparator:

Reducing blood loss after hip and knee arthroplasty helps patients avoid anaemia and allogenic blood transfusion with their incumbent risks. Tranexamic acid (TXA) is effective at reducing blood loss in elective joint arthroplasty, but there is no accepted protocol for the most effective way to administer TXA. It remains unclear as to whether extending a dosing regime of TXA beyond the immediate perioperative period would lead to further reductions in blood loss. Oral TXA would be a cheaper and less labour intensive mode of delivery post-operatively than either intravenous bolus or intravenous infusion regimes. TRAC-24 aims aim to maximise the potential of TXA by continuing administration post-operatively, at the time of greatest loss.
The efficacy of TXA will be assessed in a large group of patients, including those at risk of venous or atrierial thrombotic events, undergoing primary hip or knee arthroplasty. This study will allocate patients to one of three groups, two TXA intervention groups (Groups 1 & 2) and one non-treatment group (Control Group 3). Randomisation to Group 3 was stopped after the Interim Analysis following DMEC recommendations. The primary objective of TRAC-24 is to determine if the use of oral tranexamic acid post-operatively for up to 24h hours will confer a reduction in calculated blood loss at 48 hours beyond an intra-operative intravenous bolus alone for patients undergoing unilateral primary total hip or knee replacement. The secondary objective is to determine if the addition of oral TXA post-operatively to an intra-operative intravenous bolus of TXA produces any change in other measurable parameters as compared to those observed either with an intra-operative intravenous bolus alone or no TXA for patients undergoing unilateral primary THA/TKA.

Actual start date of recruitment	07 July 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Scientific research
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1086
Worldwide total number of subjects	1086
EEA total number of subjects	1086

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)	402
From 65 to 84 years	662
85 years and over	22

Subject disposition

Recruitment

Recruitment details:

TRAC-24 is a single site study, opened at Primary Joint Unit, Musgrave Park Hospital Belfast in June 2016. Recruitment started in July 2016 and was completed in July 2019.

Pre-assignment

Screening details:

Patients were screened for eligibility based on the inclusion/exclusion criteria outlined in trial protocol. Eligibility was confirmed by a medically qualified doctor and the inclusion criteria related to those awaiting primary elective hip or knee replacement within the age group of >18 years of age and ≤100 years.

Pre-assignment period milestones

Number of subjects started	1554[1]
Number of subjects completed	1086

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Inclusion/Exclusion criteria not met: 468

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 1086 patients enrolled as per the worldwide number enrolled.
Pre-assignment period (i.e. Screening) - number started 1554 with 1086 completed (i.e. 1086 enrolled at the end of screening)

Period 1

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

Blinding implementation details:

Anaesthetists, surgeons, other theatre, recovery and ward staff will not be blinded to the treatment, nor will the study investigators or the patient themselves. Ward staff, recovery staff and patients will be aware of which group each trial patient is in namely; intervention group 1, intervention group 2 or control group 3.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention Group 1

Arm description:

1g IV TXA peri-operatively plus 1g oral TXA every 8hrs for up to 24hrs

Arm type	Active comparator
Investigational medicinal product name	Tranexamic acid
Investigational medicinal product code	
Other name	TXA
Pharmaceutical forms	Tablet, Solution for injection/infusion
Routes of administration	Oral use, Intravenous bolus use

Dosage and administration details:

The IV dose 1g should be administered intra-operatively by slow intravenous injection at 0h within 30 minutes before KTS, and oral 1g doses should be administered within a ±2 hour window at 2h, 10h, 18h and 26h.
For patients with raised creatinine levels; 120-249 µmol/L administer TXA IV 0.5g at 0h, TXA oral 0.5g

at 2h, 10h, 18h and 26h, 250 – 499 µmol/L administer TXA IV 0.5g at 0h, TXA oral 0.5g at 10h and 26h, and for ≥500 µmol/L administer TXA IV 0.5g at 0h, TXA oral 0.5g at 26h.

Arm title	Intervention Group 2
Arm description:	
Intra-operative IV TXA within 30 mins before KTS or application of tourniquet. Patients with a renal impairment will receive a reduced dose dependent on pre- operative serum creatinine.	
Arm type	Active comparator
Investigational medicinal product name	Tranexamic acid
Investigational medicinal product code	
Other name	TXA
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous bolus use
Dosage and administration details:	
The IV dose 1g should be administered intra-operatively by slow intravenous injection at 0h within 30 minutes before KTS. For patients with raised creatinine levels ≥120 µmol/L administer TXA IV 0.5g at 0h.	

Arm title	Control Group 3
Arm description:	
Standard care_no intervention	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Intervention Group 1	Intervention Group 2	Control Group 3
Started	474	478	134
Completed	473	478	134
Not completed	1	0	0
Patient ineligible, randomised in error	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Intervention Group 1
Reporting group description:	
1g IV TXA peri-operatively plus 1g oral TXA every 8hrs for up to 24hrs	
Reporting group title	Intervention Group 2
Reporting group description:	
Intra-operative IV TXA within 30 mins before KTS or application of tourniquet. Patients with a renal impairment will receive a reduced dose dependent on pre- operative serum creatinine.	
Reporting group title	Control Group 3
Reporting group description:	
Standard care_no intervention	

Reporting group values	Intervention Group 1	Intervention Group 2	Control Group 3
Number of subjects	474	478	134
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)	181	170	51
From 65-84 years	284	297	81
85 years and over	9	11	2
Age continuous Units: years			
arithmetic mean	67.1	68.0	67.4
standard deviation	± 10.4	± 10.4	± 10.6
Gender categorical Units: Subjects			
Female	255	278	76
Male	218	200	58
Not Recorded	1	0	0
Pre-op Creatinine Level Units: Subjects			
Normal (<120 µmol/L)	456	460	128
High A (120-249 µmol/L)	17	17	5
High B (250-499 µmol/L)	0	1	0
High C (≥500 µmol/L)	0	0	1
Not Recorded	1	0	0
Surgeon Units: Subjects			
David Beverland	244	248	72
Seamus O'Hagan	123	122	33

Dennis Molloy	51	50	16
Brian Mockford	55	58	13
Not Recorded	1	0	0
Joint Units: Subjects			
Hip	233	235	66
Knee	240	243	68
Not Recorded	1	0	0
History of IHD Units: Subjects			
Yes	69	60	13
No	402	418	121
Not Recorded	3	0	0
History of COPD Units: Subjects			
Yes	34	32	5
No	437	446	129
Not Recorded	3	0	0
Is the patient a smoker? Units: Subjects			
Yes	49	40	10
No	422	438	124
Not Recorded	3	0	0
History of VTE Units: Subjects			
Yes	24	18	9
No	447	460	125
Not Recorded	3	0	0
History of MI Units: Subjects			
Yes	37	28	7
No	434	450	127
Not Recorded	3	0	0
History of Cardiac Stent Units: Subjects			
Yes	29	30	4
No	442	448	130
Not Recorded	3	0	0
History of TI Units: Subjects			
Yes	17	15	6
No	454	463	128
Not Recorded	3	0	0
History of Stroke Units: Subjects			
Yes	5	6	1
No	466	472	133
Not Recorded	3	0	0
Diabetes Units: Subjects			
Yes	51	76	22

No	420	402	112
Not Recorded	3	0	0

BMI			
Units: kg/m2			
arithmetic mean	31.4	31.4	31.6
standard deviation	± 5.4	± 5.9	± 5.5
Pre-op Haemoglobin			
Units: g/L			
arithmetic mean	137.1	135.7	136.7
standard deviation	± 13.6	± 13.1	± 12.5
Pre-op Haematocrit			
Units: L/L			
arithmetic mean	0.41	0.40	0.40
standard deviation	± 0.04	± 0.04	± 0.03
Pre-op Platelets			
Units: mm³			
arithmetic mean	255.6	260.7	253.9
standard deviation	± 66.0	± 65.4	± 59.5
Pre-op CRP			
Units: mg/l			
arithmetic mean	4.6	4.8	5.5
standard deviation	± 6.6	± 8.1	± 9.6
Pre-op Creatinine Level			
Units: µmol/L			
arithmetic mean	82.0	82.2	85.2
standard deviation	± 19.6	± 21.1	± 52.9
Pre-op OHS			
Units: N/A			
arithmetic mean	46.6	46.6	45.4
standard deviation	± 6.8	± 7.3	± 6.0
Pre-op OKS			
Units: N/A			
arithmetic mean	44.4	44.9	45.3
standard deviation	± 6.8	± 6.8	± 6.7

Reporting group values	Total		
Number of subjects	1086		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	402		
From 65-84 years	662		
85 years and over	22		

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	609		
Male	476		
Not Recorded	1		
Pre-op Creatinine Level Units: Subjects			
Normal (<120 µmol/L)	1044		
High A (120-249 µmol/L)	39		
High B (250-499 µmol/L)	1		
High C (≥500 µmol/L)	1		
Not Recorded	1		
Surgeon Units: Subjects			
David Beverland	564		
Seamus O'Hagan	278		
Dennis Molloy	117		
Brian Mockford	126		
Not Recorded	1		
Joint Units: Subjects			
Hip	534		
Knee	551		
Not Recorded	1		
History of IHD Units: Subjects			
Yes	142		
No	941		
Not Recorded	3		
History of COPD Units: Subjects			
Yes	71		
No	1012		
Not Recorded	3		
Is the patient a smoker? Units: Subjects			
Yes	99		
No	984		
Not Recorded	3		
History of VTE Units: Subjects			
Yes	51		
No	1032		
Not Recorded	3		
History of MI Units: Subjects			
Yes	72		

No	1011		
Not Recorded	3		
History of Cardiac Stent Units: Subjects			
Yes	63		
No	1020		
Not Recorded	3		
History of TI Units: Subjects			
Yes	38		
No	1045		
Not Recorded	3		
History of Stroke Units: Subjects			
Yes	12		
No	1071		
Not Recorded	3		
Diabetes Units: Subjects			
Yes	149		
No	934		
Not Recorded	3		
BMI Units: kg/m2 arithmetic mean standard deviation	- -		
Pre-op Haemoglobin Units: g/L arithmetic mean standard deviation	- -		
Pre-op Haematocrit Units: L/L arithmetic mean standard deviation	- -		
Pre-op Platelets Units: mm³ arithmetic mean standard deviation	- -		
Pre-op CRP Units: mg/l arithmetic mean standard deviation	- -		
Pre-op Creatinine Level Units: µmol/L arithmetic mean standard deviation	- -		
Pre-op OHS Units: N/A arithmetic mean standard deviation	- -		
Pre-op OKS			

Units: N/A arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Intervention Group 1
Reporting group description:	
1g IV TXA peri-operatively plus 1g oral TXA every 8hrs for up to 24hrs	
Reporting group title	Intervention Group 2
Reporting group description:	
Intra-operative IV TXA within 30 mins before KTS or application of tourniquet. Patients with a renal impairment will receive a reduced dose dependent on pre- operative serum creatinine.	
Reporting group title	Control Group 3
Reporting group description:	
Standard care_no intervention	

Primary: Primary Outcome

End point title	Primary Outcome
End point description:	
Indirect blood loss at 48 hours	
End point type	Primary
End point timeframe:	
48 Hours	

End point values	Intervention Group 1	Intervention Group 2	Control Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	456	454	133	
Units: Millilitres				
arithmetic mean (standard deviation)	790.4 (± 428.8)	851.7 (± 423.1)	1282.4 (± 592.0)	

Statistical analyses

Statistical analysis title	All Patients - 1vs2
Comparison groups	Intervention Group 1 v Intervention Group 2
Number of subjects included in analysis	910
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-61.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-116.7
upper limit	-5.8

Statistical analysis title	All Patients - 1vs2 (Adjusted)
Statistical analysis description: adjusted for age, weight, surgeon and recruitment period	
Comparison groups	Intervention Group 1 v Intervention Group 2
Number of subjects included in analysis	910
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-71.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-124.7
upper limit	-18.5

Statistical analysis title	All Patients - 1vs2vs3
Comparison groups	Intervention Group 1 v Intervention Group 2 v Control Group 3
Number of subjects included in analysis	1043
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA

Statistical analysis title	All Patients - combined vs 3
Comparison groups	Intervention Group 1 v Intervention Group 2 v Control Group 3
Number of subjects included in analysis	1043
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	461.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	379.2
upper limit	534.6

Notes:

[1] - Comparing the primary outcome for both intervention groups combined against the control group

Secondary: Secondary: Incidence of post-operative Hb falling below the transfusion trigger (irrespective of transfusion) prior to discharge

End point title	Secondary: Incidence of post-operative Hb falling below the transfusion trigger (irrespective of transfusion) prior to discharge

End point description:

End point type	Secondary

End point timeframe:

Prior to discharge

End point values	Intervention Group 1	Intervention Group 2	Control Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	471	476	134	
Units: Numbers	16	28	12	

Statistical analyses

Statistical analysis title	All Patients - 1vs2vs3
Comparison groups	Intervention Group 1 v Intervention Group 2 v Control Group 3
Number of subjects included in analysis	1081
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025 [2]
Method	Chi-squared

Notes:

[2] - post-hoc comparison of group 1 vs group 2 p=0.07

Secondary: Secondary: Change in Creatinine level pre-surgery to 48 hours post-surgery

End point title	Secondary: Change in Creatinine level pre-surgery to 48 hours post-surgery

End point description:

End point type	Secondary

End point timeframe:

48 hours post-surgery

End point values	Intervention Group 1	Intervention Group 2	Control Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	461	453	131	
Units: µmol/l				
arithmetic mean (standard deviation)	-2.9 (± 10.8)	-3.2 (± 12.5)	-2.5 (± 12.6)	

Statistical analyses

Statistical analysis title	All Patients - 1vs2vs3
Statistical analysis description: Change is calculated as 48hr minus pre-op.	
Comparison groups	Intervention Group 2 v Control Group 3 v Intervention Group 1
Number of subjects included in analysis	1045
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81
Method	ANOVA

Secondary: Secondary: 90 day mortality

End point title	Secondary: 90 day mortality
End point description:	
End point type	Secondary
End point timeframe: 90 day	

End point values	Intervention Group 1	Intervention Group 2	Control Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	471	476	134	
Units: Number	1	0	1	

Statistical analyses

Statistical analysis title	All Patients - 1vs2vs3
Comparison groups	Intervention Group 1 v Intervention Group 2 v Control Group 3

Number of subjects included in analysis	1081
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Fisher exact

Secondary: Secondary: 1 year mortality

End point title	Secondary: 1 year mortality

End point description:

End point type	Secondary

End point timeframe:

1 year

End point values	Intervention Group 1	Intervention Group 2	Control Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	471	476	134	
Units: Number	5	3	3	

Statistical analyses

Statistical analysis title	All Patients- 1vs2vs3
Comparison groups	Intervention Group 1 v Intervention Group 2 v Control Group 3
Number of subjects included in analysis	1081
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.23
Method	Fisher exact

Secondary: Secondary: Change in c-reactive protein pre-surgery to 48 hours post-surgery

End point title	Secondary: Change in c-reactive protein pre-surgery to 48 hours post-surgery

End point description:

End point type	Secondary

End point timeframe:

48 hours post-surgery

End point values	Intervention Group 1	Intervention Group 2	Control Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	428	411	115	
Units: mg/l				
arithmetic mean (standard deviation)	119.6 (± 80.9)	113.0 (± 75.9)	111.1 (± 68.4)	

Statistical analyses

Statistical analysis title	All Patients - 1vs2vs3
Comparison groups	Intervention Group 1 v Intervention Group 2 v Control Group 3
Number of subjects included in analysis	954
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	ANOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE reporting period for the trial begins upon enrolment into the trial and ends 30 days following the last administration of the study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	4

Reporting groups

Reporting group title	Intervention Group 1

Reporting group description:

1g IV TXA peri-operatively plus 1g oral TXA every 8hrs for up to 24hrs

Reporting group title	Intervention Group 2

Reporting group description:

Intra-operative IV TXA within 30 mins before KTS or application of tourniquet. Patients with a renal impairment will receive a reduced dose dependent on pre- operative serum creatinine.

Reporting group title	Control Group 3

Reporting group description:

Standard care_no intervention

Serious adverse events	Intervention Group 1	Intervention Group 2	Control Group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 473 (8.03%)	50 / 478 (10.46%)	19 / 134 (14.18%)
number of deaths (all causes)	5	3	3
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic mass and multiple liver metastases			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hematoma			
subjects affected / exposed	0 / 473 (0.00%)	0 / 478 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thromboembolic Event			
subjects affected / exposed	1 / 473 (0.21%)	3 / 478 (0.63%)	3 / 134 (2.24%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Implant Malposition			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 473 (0.00%)	3 / 478 (0.63%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	2 / 473 (0.42%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other-General Disorders and Administration Site Conditions			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 473 (0.00%)	0 / 478 (0.00%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			

subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	1 / 473 (0.21%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other - Psychiatric Disorders			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip dislocation			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal Fracture			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound Complication			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other - Injury, poisoning and procedural complications			
subjects affected / exposed	1 / 473 (0.21%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Heart Failure			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other - Cardiac Disorders			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Tachycardia			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Other-Nervous System Disorders			
subjects affected / exposed	0 / 473 (0.00%)	0 / 478 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 473 (0.00%)	0 / 478 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	2 / 473 (0.42%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stroke			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	3 / 473 (0.63%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic Perforation			
subjects affected / exposed	0 / 473 (0.00%)	0 / 478 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Constipation			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Duodenal Obstruction			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large Bowel Obstruction			
subjects affected / exposed	0 / 473 (0.00%)	0 / 478 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 473 (0.21%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney injury			
subjects affected / exposed	2 / 473 (0.42%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hematuria			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uriary Retention			
subjects affected / exposed	1 / 473 (0.21%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Bruising			
subjects affected / exposed	0 / 473 (0.00%)	0 / 478 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dislocation			
subjects affected / exposed	2 / 473 (0.42%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint Effusion			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint Range of Motion Decreased			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Joint Infection			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Infection			
subjects affected / exposed	0 / 473 (0.00%)	3 / 478 (0.63%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Infection			
subjects affected / exposed	3 / 473 (0.63%)	2 / 478 (0.42%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Wound Infection			
subjects affected / exposed	0 / 473 (0.00%)	0 / 478 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesemia			
subjects affected / exposed	0 / 473 (0.00%)	0 / 478 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	13 / 473 (2.75%)	16 / 478 (3.35%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 13	0 / 16	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other - Metabolism and Nutrition			
subjects affected / exposed	1 / 473 (0.21%)	2 / 478 (0.42%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Intervention Group 1	Intervention Group 2	Control Group 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	294 / 473 (62.16%)	311 / 478 (65.06%)	79 / 134 (58.96%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 473 (0.42%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	2	0	0
Hypervolemia			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Hypotension			

subjects affected / exposed	3 / 473 (0.63%)	6 / 478 (1.26%)	2 / 134 (1.49%)
occurrences (all)	3	6	2
Thromboembolic event			
subjects affected / exposed	0 / 473 (0.00%)	0 / 478 (0.00%)	1 / 134 (0.75%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 473 (0.00%)	0 / 478 (0.00%)	1 / 134 (0.75%)
occurrences (all)	0	0	1
Non Cardiac Chest Pain			
subjects affected / exposed	3 / 473 (0.63%)	4 / 478 (0.84%)	3 / 134 (2.24%)
occurrences (all)	3	4	3
Oedema Limbs			
subjects affected / exposed	0 / 473 (0.00%)	2 / 478 (0.42%)	0 / 134 (0.00%)
occurrences (all)	0	2	0
Pain			
subjects affected / exposed	1 / 473 (0.21%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	1	1	0
Pruritus			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	0	1	0
Wound infection			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Allergic Reaction			
subjects affected / exposed	2 / 473 (0.42%)	2 / 478 (0.42%)	1 / 134 (0.75%)
occurrences (all)	2	2	1
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 473 (0.21%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	1	1	0
Epistaxis			

subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Hiccups			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Hypoxemia			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Hypoxia			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Sleep Apnea			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Confusion			
subjects affected / exposed	8 / 473 (1.69%)	3 / 478 (0.63%)	0 / 134 (0.00%)
occurrences (all)	8	3	0
Delirium			
subjects affected / exposed	2 / 473 (0.42%)	5 / 478 (1.05%)	0 / 134 (0.00%)
occurrences (all)	2	5	0
Investigations			
Echocardiography			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Ultrasound Liver			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	9 / 473 (1.90%)	11 / 478 (2.30%)	2 / 134 (1.49%)
occurrences (all)	10	11	2
Fracture			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Prosthesis Subluxation			

subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	0	1	0
Subluxation			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Wound Complication			
subjects affected / exposed	1 / 473 (0.21%)	1 / 478 (0.21%)	1 / 134 (0.75%)
occurrences (all)	1	1	1
Wound Dehiscence			
subjects affected / exposed	1 / 473 (0.21%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	1	1	0
Cardiac disorders			
Atrial Fibrilation			
subjects affected / exposed	3 / 473 (0.63%)	3 / 478 (0.63%)	3 / 134 (2.24%)
occurrences (all)	3	3	3
Chest Pain - Cardiac			
subjects affected / exposed	1 / 473 (0.21%)	2 / 478 (0.42%)	1 / 134 (0.75%)
occurrences (all)	1	2	1
Ectopics			
subjects affected / exposed	2 / 473 (0.42%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	2	0	0
Hypotension			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Ischemia			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	0	1	0
Sinus Bradycardia			
subjects affected / exposed	8 / 473 (1.69%)	9 / 478 (1.88%)	2 / 134 (1.49%)
occurrences (all)	8	9	2
Sinus Tachycardia			
subjects affected / exposed	7 / 473 (1.48%)	8 / 478 (1.67%)	0 / 134 (0.00%)
occurrences (all)	7	8	0
Tachycardia			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0

Ventricular arrhythmia			
subjects affected / exposed	4 / 473 (0.85%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	4	0	0
Ventricular fibrillation			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 473 (4.02%)	25 / 478 (5.23%)	4 / 134 (2.99%)
occurrences (all)	19	25	4
Dizziness/Vasovagal Reaction			
subjects affected / exposed	10 / 473 (2.11%)	19 / 478 (3.97%)	1 / 134 (0.75%)
occurrences (all)	10	19	1
Headache			
subjects affected / exposed	1 / 473 (0.21%)	3 / 478 (0.63%)	0 / 134 (0.00%)
occurrences (all)	1	3	0
Memory impairment			
subjects affected / exposed	0 / 473 (0.00%)	0 / 478 (0.00%)	1 / 134 (0.75%)
occurrences (all)	0	0	1
Nervous System Disorder			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	0	1	0
Other - Non specific Numbness			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	1 / 473 (0.21%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	1	1	0
Somnolence			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Vasovagal Reaction			

subjects affected / exposed	57 / 473 (12.05%)	60 / 478 (12.55%)	22 / 134 (16.42%)
occurrences (all)	57	61	23
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 473 (0.63%)	6 / 478 (1.26%)	9 / 134 (6.72%)
occurrences (all)	3	10	11
Eye disorders			
Blurred Vision			
subjects affected / exposed	2 / 473 (0.42%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	2	1	0
Conjunctivitis			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	0	1	0
Anal Haemorrhage			
subjects affected / exposed	0 / 473 (0.00%)	0 / 478 (0.00%)	1 / 134 (0.75%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	2 / 473 (0.42%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	2	1	0
Diarrhea			
subjects affected / exposed	4 / 473 (0.85%)	3 / 478 (0.63%)	1 / 134 (0.75%)
occurrences (all)	4	3	1
Dry Mouth			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	3 / 473 (0.63%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	4	0	0
Gastric Haemorrhage			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Gastroesophageal Reflux Disease			

subjects affected / exposed	0 / 473 (0.00%)	3 / 478 (0.63%)	0 / 134 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	93 / 473 (19.66%)	100 / 478 (20.92%)	22 / 134 (16.42%)
occurrences (all)	93	100	28
Nausea/Vomiting			
subjects affected / exposed	52 / 473 (10.99%)	60 / 478 (12.55%)	13 / 134 (9.70%)
occurrences (all)	52	60	13
Vomiting			
subjects affected / exposed	19 / 473 (4.02%)	25 / 478 (5.23%)	6 / 134 (4.48%)
occurrences (all)	19	25	6
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	27 / 473 (5.71%)	25 / 478 (5.23%)	1 / 134 (0.75%)
occurrences (all)	27	25	1
Allergic Reaction			
subjects affected / exposed	0 / 473 (0.00%)	0 / 478 (0.00%)	1 / 134 (0.75%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	11 / 473 (2.33%)	12 / 478 (2.51%)	4 / 134 (2.99%)
occurrences (all)	11	12	4
Haematuria			
subjects affected / exposed	1 / 473 (0.21%)	2 / 478 (0.42%)	1 / 134 (0.75%)
occurrences (all)	1	2	1
Poor Urinary output			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	0	1	0
Urinary Retention			
subjects affected / exposed	1 / 473 (0.21%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Bruising			
subjects affected / exposed	1 / 473 (0.21%)	2 / 478 (0.42%)	0 / 134 (0.00%)
occurrences (all)	1	2	0
Dislocation			

subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	2	0	0
Hip Pain			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Joint range of motion decreased			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 473 (0.00%)	2 / 478 (0.42%)	0 / 134 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Joint Infection			
subjects affected / exposed	1 / 473 (0.21%)	0 / 478 (0.00%)	0 / 134 (0.00%)
occurrences (all)	1	0	0
Lower respiratory infections			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	0	1	0
Lung Infection			
subjects affected / exposed	3 / 473 (0.63%)	4 / 478 (0.84%)	2 / 134 (1.49%)
occurrences (all)	3	4	2
Paronychia			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	0	1	0
Skin Infection			
subjects affected / exposed	2 / 473 (0.42%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	2	1	0
Upper Respiratory Infections			
subjects affected / exposed	1 / 473 (0.21%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	0 / 473 (0.00%)	2 / 478 (0.42%)	0 / 134 (0.00%)
occurrences (all)	0	2	0
Wound Infection			
subjects affected / exposed	1 / 473 (0.21%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	1	1	0

Metabolism and nutrition disorders			
Hyperkalemia			
subjects affected / exposed	0 / 473 (0.00%)	1 / 478 (0.21%)	0 / 134 (0.00%)
occurrences (all)	0	1	0
Hypokalemia			
subjects affected / exposed	2 / 473 (0.42%)	1 / 478 (0.21%)	2 / 134 (1.49%)
occurrences (all)	2	1	2
Hyponatremia			
subjects affected / exposed	22 / 473 (4.65%)	23 / 478 (4.81%)	10 / 134 (7.46%)
occurrences (all)	23	23	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2016	An amendment to protocol to include clarification of the background and equations for the total indirect blood loss, changes made to the screening procedure for patient recruitment and addition of details for the interim analysis.
03 February 2017	An amendment to the protocol was submitted as an action following an Urgent Safety Measure (procedures to ensure that all blood results are clinically reviewed, changes to exclusion criteria, details of co-investigators, logistics of obtaining research blood samples and clarification of additional blood tests.
22 June 2017	This protocol change was to address the DMEC recommendation to terminate the randomisation of pateints to Control Group 3 of the study.
18 September 2018	An amendment to for cater for the request access to patient records held on electronically retrospectively and in the future.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported