



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 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 arterial 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/m ² arithmetic mean standard deviation | 31.4 ± 5.4 | 31.4 ± 5.9 | 31.6 ± 5.5 |
| Pre-op Haemoglobin Units: g/L arithmetic mean standard deviation | 137.1 ± 13.6 | 135.7 ± 13.1 | 136.7 ± 12.5 |
| Pre-op Haematocrit Units: L/L arithmetic mean standard deviation | 0.41 ± 0.04 | 0.40 ± 0.04 | 0.40 ± 0.03 |
| Pre-op Platelets Units: mm ³ arithmetic mean standard deviation | 255.6 ± 66.0 | 260.7 ± 65.4 | 253.9 ± 59.5 |
| Pre-op CRP Units: mg/l arithmetic mean standard deviation | 4.6 ± 6.6 | 4.8 ± 8.1 | 5.5 ± 9.6 |
| Pre-op Creatinine Level Units: µmol/L arithmetic mean standard deviation | 82.0 ± 19.6 | 82.2 ± 21.1 | 85.2 ± 52.9 |
| Pre-op OHS Units: N/A arithmetic mean standard deviation | 46.6 ± 6.8 | 46.6 ± 7.3 | 45.4 ± 6.0 |
| Pre-op OKS Units: N/A arithmetic mean standard deviation | 44.4 ± 6.8 | 44.9 ± 6.8 | 45.3 ± 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 Not Recorded | 1011 3 | | |
| History of Cardiac Stent Units: Subjects | | | |
| Yes No Not Recorded | 63 1020 3 | | |
| History of TI Units: Subjects | | | |
| Yes No Not Recorded | 38 1045 3 | | |
| History of Stroke Units: Subjects | | | |
| Yes No Not Recorded | 12 1071 3 | | |
| Diabetes Units: Subjects | | | |
| Yes No Not Recorded | 149 934 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: mm ³ 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 occurrences (all) | 3 / 473 (0.63%) 3 | 6 / 478 (1.26%) 6 | 2 / 134 (1.49%) 2 |
| Thromboembolic event subjects affected / exposed occurrences (all) | 0 / 473 (0.00%) 0 | 0 / 478 (0.00%) 0 | 1 / 134 (0.75%) 1 |
| General disorders and administration site conditions | | | |
| Fever subjects affected / exposed occurrences (all) | 0 / 473 (0.00%) 0 | 1 / 478 (0.21%) 1 | 0 / 134 (0.00%) 0 |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 0 / 473 (0.00%) 0 | 0 / 478 (0.00%) 0 | 1 / 134 (0.75%) 1 |
| Non Cardiac Chest Pain subjects affected / exposed occurrences (all) | 3 / 473 (0.63%) 3 | 4 / 478 (0.84%) 4 | 3 / 134 (2.24%) 3 |
| Oedema Limbs subjects affected / exposed occurrences (all) | 0 / 473 (0.00%) 0 | 2 / 478 (0.42%) 2 | 0 / 134 (0.00%) 0 |
| Pain subjects affected / exposed occurrences (all) | 1 / 473 (0.21%) 1 | 1 / 478 (0.21%) 1 | 0 / 134 (0.00%) 0 |
| Pruritus subjects affected / exposed occurrences (all) | 0 / 473 (0.00%) 0 | 1 / 478 (0.21%) 1 | 0 / 134 (0.00%) 0 |
| Wound infection subjects affected / exposed occurrences (all) | 1 / 473 (0.21%) 1 | 0 / 478 (0.00%) 0 | 0 / 134 (0.00%) 0 |
| Immune system disorders | | | |
| Allergic Reaction subjects affected / exposed occurrences (all) | 2 / 473 (0.42%) 2 | 2 / 478 (0.42%) 2 | 1 / 134 (0.75%) 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Atelectasis subjects affected / exposed occurrences (all) | 1 / 473 (0.21%) 1 | 1 / 478 (0.21%) 1 | 0 / 134 (0.00%) 0 |
| Epistaxis | | | |

| | | | |
|--|-----------------------|------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 473 (0.21%) 1 | 0 / 478 (0.00%) 0 | 0 / 134 (0.00%) 0 |
| Hiccups | | | |
| subjects affected / exposed occurrences (all) | 1 / 473 (0.21%) 1 | 0 / 478 (0.00%) 0 | 0 / 134 (0.00%) 0 |
| Hypoxemia | | | |
| subjects affected / exposed occurrences (all) | 1 / 473 (0.21%) 1 | 0 / 478 (0.00%) 0 | 0 / 134 (0.00%) 0 |
| Hypoxia | | | |
| subjects affected / exposed occurrences (all) | 1 / 473 (0.21%) 1 | 0 / 478 (0.00%) 0 | 0 / 134 (0.00%) 0 |
| Sleep Apnea | | | |
| subjects affected / exposed occurrences (all) | 0 / 473 (0.00%) 0 | 1 / 478 (0.21%) 1 | 0 / 134 (0.00%) 0 |
| Psychiatric disorders | | | |
| Confusion | | | |
| subjects affected / exposed occurrences (all) | 8 / 473 (1.69%) 8 | 3 / 478 (0.63%) 3 | 0 / 134 (0.00%) 0 |
| Delirium | | | |
| subjects affected / exposed occurrences (all) | 2 / 473 (0.42%) 2 | 5 / 478 (1.05%) 5 | 0 / 134 (0.00%) 0 |
| Investigations | | | |
| Echocardiography | | | |
| subjects affected / exposed occurrences (all) | 1 / 473 (0.21%) 1 | 0 / 478 (0.00%) 0 | 0 / 134 (0.00%) 0 |
| Ultrasound Liver | | | |
| subjects affected / exposed occurrences (all) | 1 / 473 (0.21%) 1 | 0 / 478 (0.00%) 0 | 0 / 134 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed occurrences (all) | 9 / 473 (1.90%) 10 | 11 / 478 (2.30%) 11 | 2 / 134 (1.49%) 2 |
| Fracture | | | |
| subjects affected / exposed occurrences (all) | 1 / 473 (0.21%) 1 | 0 / 478 (0.00%) 0 | 0 / 134 (0.00%) 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 Fibrillation | | | |
| 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 occurrences (all) | 4 / 473 (0.85%) 4 | 0 / 478 (0.00%) 0 | 0 / 134 (0.00%) 0 |
| Ventricular fibrillation subjects affected / exposed occurrences (all) | 1 / 473 (0.21%) 1 | 0 / 478 (0.00%) 0 | 0 / 134 (0.00%) 0 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 19 / 473 (4.02%) 19 | 25 / 478 (5.23%) 25 | 4 / 134 (2.99%) 4 |
| Dizziness/Vasovagal Reaction subjects affected / exposed occurrences (all) | 10 / 473 (2.11%) 10 | 19 / 478 (3.97%) 19 | 1 / 134 (0.75%) 1 |
| Headache subjects affected / exposed occurrences (all) | 1 / 473 (0.21%) 1 | 3 / 478 (0.63%) 3 | 0 / 134 (0.00%) 0 |
| Memory impairment subjects affected / exposed occurrences (all) | 0 / 473 (0.00%) 0 | 0 / 478 (0.00%) 0 | 1 / 134 (0.75%) 1 |
| Nervous System Disorder subjects affected / exposed occurrences (all) | 0 / 473 (0.00%) 0 | 1 / 478 (0.21%) 1 | 0 / 134 (0.00%) 0 |
| Other - Non specific Numbness subjects affected / exposed occurrences (all) | 0 / 473 (0.00%) 0 | 1 / 478 (0.21%) 0 | 0 / 134 (0.00%) 0 |
| Paraesthesia subjects affected / exposed occurrences (all) | 1 / 473 (0.21%) 1 | 1 / 478 (0.21%) 1 | 0 / 134 (0.00%) 0 |
| Somnolence subjects affected / exposed occurrences (all) | 0 / 473 (0.00%) 0 | 1 / 478 (0.21%) 1 | 0 / 134 (0.00%) 0 |
| Tremor subjects affected / exposed occurrences (all) | 1 / 473 (0.21%) 1 | 0 / 478 (0.00%) 0 | 0 / 134 (0.00%) 0 |
| Vasovagal Reaction | | | |

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

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