



## Clinical trial results:

### Tranexamic Acid for the treatment of significant traumatic brain injury: an international, randomised, double blind, placebo controlled trial.

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2011-003669-14   |
| Trial protocol           | ES GB IT IE SI   |
| Global end of trial date | 28 February 2019 |

#### Results information

|                                   |   |
|-----------------------------------|---|
| Result version number             | v1 (current)  |
| This version publication date     | 02 July 2020  |
| First version publication date    | 02 July 2020  |
| Summary attachment (see zip file) | CRASH-3_The Lancet (CRASH-3 publication.pdf)<br>CRASH-3_The Lancet figures (CRASH-3 figures.ppt)<br>CRASH-3_The Lancet supplementary files (CRASH-3_The Lancet_Supplementary files.pdf) |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | ISRCTN15088122 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN15088122 |
| ClinicalTrials.gov id (NCT number) | NCT01402882    |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | London School Of Hygiene and Tropical Medicine   |
| Sponsor organisation address | Keppel Street, London, United Kingdom, WC1E 7HT  |
| Public contact               | Haleema Shakur-Still, London School Of Hygiene and Tropical Medicine, +44 2079588113, haleema.shakur-still@lshtm.ac.uk |
| Scientific contact           | Ian Roberts, London School Of Hygiene and Tropical Medicine, +44 2079588128, haleema.shakur-still@lshtm.ac.uk          |

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                       | 30 May 2019      |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 28 February 2019 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 28 February 2019 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The CRASH-3 trial will see if a drug called tranexamic acid will improve outcomes for people who have suffered a traumatic head injury. The main outcome is its effect on death within 28 days of the head injury among patients randomised within 3 hours of injury. We will also assess the cause of death.

Protection of trial subjects:

The trial was done in accordance with the good clinical practice guidelines by the International Conference on Harmonisation. The procedure at each site was approved by the relevant ethics committee and regulatory agencies. Consent was obtained from participants if their physical and mental capacity allowed (as judged by the treating clinician). If a participant was unable to give consent, proxy consent was obtained from a relative or representative. If a proxy was unavailable, then if permitted by local regulation, consent was waived. When consent was waived or given by a proxy, the participant was informed about the trial as soon as possible, and consent was obtained for ongoing data collection, if needed.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 20 July 2012 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                      |
|--------------------------------------|----------------------|
| Country: Number of subjects enrolled | Romania: 35          |
| Country: Number of subjects enrolled | Slovenia: 15         |
| Country: Number of subjects enrolled | Spain: 425           |
| Country: Number of subjects enrolled | United Kingdom: 3143 |
| Country: Number of subjects enrolled | Ireland: 12          |
| Country: Number of subjects enrolled | Italy: 72            |
| Country: Number of subjects enrolled | Afghanistan: 87      |
| Country: Number of subjects enrolled | Albania: 214         |
| Country: Number of subjects enrolled | Cambodia: 45         |
| Country: Number of subjects enrolled | Cameroon: 116        |
| Country: Number of subjects enrolled | Canada: 7            |
| Country: Number of subjects enrolled | Colombia: 335        |
| Country: Number of subjects enrolled | Egypt: 20            |
| Country: Number of subjects enrolled | El Salvador: 28      |
| Country: Number of subjects enrolled | Indonesia: 6         |
| Country: Number of subjects enrolled | Iraq: 55             |

|                                      |                           |
|--------------------------------------|---------------------------|
| Country: Number of subjects enrolled | Jamaica: 7                |
| Country: Number of subjects enrolled | Japan: 165                |
| Country: Number of subjects enrolled | Kenya: 1                  |
| Country: Number of subjects enrolled | Mexico: 79                |
| Country: Number of subjects enrolled | Myanmar: 121              |
| Country: Number of subjects enrolled | Nepal: 255                |
| Country: Number of subjects enrolled | Nigeria: 409              |
| Country: Number of subjects enrolled | Papua New Guinea: 10      |
| Country: Number of subjects enrolled | United Arab Emirates: 126 |
| Country: Number of subjects enrolled | Zambia: 44                |
| Country: Number of subjects enrolled | Pakistan: 4567            |
| Country: Number of subjects enrolled | Malaysia: 1567            |
| Country: Number of subjects enrolled | Georgia: 771              |
| Worldwide total number of subjects   | 12737                     |
| EEA total number of subjects         | 3702                      |

Notes:

| <b>Subjects enrolled per age group</b>    |       |
|---|-------|
| 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)                     | 3     |
| Adolescents (12-17 years)                 | 55    |
| Adults (18-64 years)                      | 10417 |
| From 65 to 84 years                       | 1895  |
| 85 years and over                         | 367   |

## Subject disposition

### Recruitment

Recruitment details:

The CRASH-3 trial randomised patients aged 16 and older with a traumatic brain injury in 175 hospitals in 29 countries.

The first patient was randomised on 20/07/2012 and the final patient on 31/01/2019.

### Pre-assignment

Screening details:

All adult patients with TBI, within 3 hours of injury, with a GCS score of 12 or lower or any intracranial bleeding on CT scan, and no major extracranial bleeding were eligible. The fundamental eligibility criterion is the responsible clinician's 'uncertainty' as to whether or not to use an antifibrinolytic agent in a particular patient with TBI.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Overall trial (overall period)                  |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                         |
| Blinding used                | Double blind                                    |
| Roles blinded                | Subject, Investigator, Monitor, Carer, Assessor |

Blinding implementation details:

Ampoules and packaging for tranexamic acid (TXA) and placebo were identical in appearance. The masking involved the removal of the original manufacturer's label and replacement with the clinical trial label bearing the randomisation number, which was used as the pack identification. Patients were randomly allocated to receive TXA or placebo. The randomisation codes were generated and held by an independent statistical consultant.

### Arms

|  |                   |
|--|-------------------|
| Are arms mutually exclusive?           | Yes               |
| <b>Arm title</b>                       | Tranexamic acid   |
| Arm description: -                     |                   |
| Arm type                               | Experimental      |
| Investigational medicinal product name | Cyklokapron       |
| Investigational medicinal product code | B02AA02           |
| Other name                             |                   |
| Pharmaceutical forms                   | Injection         |
| Routes of administration               | Intravascular use |

Dosage and administration details:

Patients were randomly allocated to receive a loading dose of 1 g of tranexamic acid or matching placebo infused over 10 min, started immediately after randomisation, followed by an intravenous infusion of 1 g over 8 h.

|  |                      |
|--|----------------------|
| <b>Arm title</b>                       | Placebo              |
| Arm description: -                     |                      |
| Arm type                               | Placebo              |
| Investigational medicinal product name | Sodium chloride 0.9% |
| Investigational medicinal product code |                      |
| Other name                             |                      |
| Pharmaceutical forms                   | Injection            |
| Routes of administration               | Intravenous use      |

Dosage and administration details:

Patients were randomly allocated to receive a loading dose of 1 g of tranexamic acid or matching placebo infused over 10 min, started immediately after randomisation, followed by an intravenous infusion of 1 g over 8 h.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Tranexamic acid | Placebo |
|---|-----------------|---------|
| Started   | 4649            | 4553    |
| Completed   | 4613            | 4514    |
| Not completed                                       | 36              | 39      |
| Consent withdrawn so outcome data unavailable       | 7               | 14      |
| Lost to follow-up                                   | 29              | 25      |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: During the trial, new research suggested that TXA was likely to only be effective within 3 hours of injury. From this point onwards, only patients within 3 hours of their injury were randomised and the primary outcome was amended to deaths among patients treated within 3 hours of injury. The total number of patients randomised worldwide is 12,737 (including all patients). The total number of patients included in the primary analysis is 9,202 (including only patients treated within 3 hours).

## Baseline characteristics

### Reporting groups

|                                |                 |
|--------------------------------|-----------------|
| Reporting group title          | Tranexamic acid |
| Reporting group description: - |                 |
| Reporting group title          | Placebo         |
| Reporting group description: - |                 |

| Reporting group values                      | Tranexamic acid | Placebo | Total |
|---|-----------------|---------|-------|
| Number of subjects                          | 4649            | 4553    | 9202  |
| Age categorical<br>Units: Subjects          |                 |         |       |
| < 25 years                                  | 1042            | 996     | 2038  |
| 25 - 44 years                               | 1716            | 1672    | 3388  |
| 45 - 64 years                               | 1169            | 1184    | 2353  |
| 65 years and over                           | 722             | 701     | 1423  |
| Gender categorical<br>Units: Subjects       |                 |         |       |
| Female                                      | 906             | 893     | 1799  |
| Male  | 3742            | 3660    | 7402  |
| Other                                       | 1               | 0       | 1     |
| Time since injury<br>Units: Subjects        |                 |         |       |
| < 1 hour                                    | 877             | 869     | 1746  |
| 1 - 2 hours                                 | 2003            | 1889    | 3892  |
| 2 - 3 hours                                 | 1769            | 1795    | 3564  |
| Systolic blood pressure<br>Units: Subjects  |                 |         |       |
| < 90 mm Hg                                  | 89              | 85      | 174   |
| 90 - 119 mm Hg                              | 1508            | 1490    | 2998  |
| 120 - 139 mm Hg                             | 1461            | 1504    | 2965  |
| 140 or over mm Hg                           | 1576            | 1466    | 3042  |
| Unknown                                     | 15              | 8       | 23    |
| Glasgow Coma Scale score<br>Units: Subjects |                 |         |       |
| GCS 3                                       | 495             | 506     | 1001  |
| GCS 4                                       | 213             | 213     | 426   |
| GCS 5                                       | 163             | 172     | 335   |
| GCS 6                                       | 221             | 232     | 453   |
| GCS 7                                       | 311             | 294     | 605   |
| GCS 8                                       | 354             | 315     | 669   |
| GCS 9                                       | 335             | 292     | 627   |
| GCS 10                                      | 371             | 364     | 735   |
| GCS 11                                      | 375             | 390     | 765   |
| GCS 12                                      | 476             | 478     | 954   |
| GCS 13                                      | 297             | 312     | 609   |
| GCS 14                                      | 526             | 458     | 984   |
| GCS 15                                      | 484             | 492     | 976   |
| Unknown                                     | 28              | 35      | 63    |

|                             |      |      |      |
|-----------------------------|------|------|------|
| Pupil Reaction              |      |      |      |
| Units: Subjects             |      |      |      |
| None reacted                | 425  | 440  | 865  |
| One reacted                 | 374  | 353  | 727  |
| Both reacted                | 3706 | 3636 | 7342 |
| Unable to assess or unknown | 144  | 124  | 268  |

## End points

### End points reporting groups

|                                |                 |
|--------------------------------|-----------------|
| Reporting group title          | Tranexamic acid |
| Reporting group description: - |                 |
| Reporting group title          | Placebo         |
| Reporting group description: - |                 |

### Primary: Effect of tranexamic acid on head injury-related death in patients randomly assigned within 3 h of injury

|                                 |   |
|---------------------------------|---|
| End point title                 | Effect of tranexamic acid on head injury-related death in patients randomly assigned within 3 h of injury |
| End point description:          |   |
| End point type                  | Primary   |
| End point timeframe:            |   |
| Within 28 days of randomisation |   |

| End point values            | Tranexamic acid | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 4613            | 4514            |  |  |
| Units: Dead or alive        | 855             | 892             |  |  |

|                            |  |
|----------------------------|--|
| Attachments (see zip file) | CRASH-3 primary analysis/CRASH-3 primary analysis.pptx |
|----------------------------|--|

### Statistical analyses

|   |                           |
|---|---------------------------|
| Statistical analysis title              | Primary analysis          |
| Comparison groups                       | Tranexamic acid v Placebo |
| Number of subjects included in analysis | 9127                      |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | superiority               |
| Parameter estimate                      | Risk ratio (RR)           |
| Point estimate                          | 0.94                      |
| Confidence interval                     |                           |
| level                                   | 95 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | 0.86                      |
| upper limit                             | 1.02                      |



**Other pre-specified: Effect of tranexamic acid on head injury-related death in patients randomly assigned within 3 h of injury excluding patients with GCS score of 3 or bilateral unreactive pupils**

|                 |   |
|-----------------|---|
| End point title | Effect of tranexamic acid on head injury-related death in patients randomly assigned within 3 h of injury excluding patients with GCS score of 3 or bilateral unreactive pupils |
|-----------------|---|

End point description:

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Within 28 days of randomisation

| End point values            | Tranexamic acid | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 3880            | 3757            |  |  |
| Units: Dead or alive        | 485             | 525             |  |  |

**Statistical analyses**

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Primary outcome: prespecified sensitivity analysis |
| Comparison groups                       | Tranexamic acid v Placebo                          |
| Number of subjects included in analysis | 7637   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| Parameter estimate                      | Risk ratio (RR)                                    |
| Point estimate                          | 0.89   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.8  |
| upper limit                             | 1  |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

A written report must be submitted within 24 hours to the Trial Coordinating Centre if any SAE, SAR or SUSAR that occurs during hospitalisation or any untoward medical occurrence after discharge and up to 28 days after the trial treatment.

Adverse event reporting additional description:

Prior to discharge, all randomised patients will be given a (supplied) alert card, so either the patient or their family can present the card to any healthcare provider they see after they are discharged.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 13.0 |
|--------------------|------|

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Tranexamic acid |
|-----------------------|-----------------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events                               | Tranexamic acid   | Placebo           |  |
|--|-------------------|-------------------|--|
| Total subjects affected by serious adverse events    |                   |                   |  |
| subjects affected / exposed                          | 76 / 6359 (1.20%) | 68 / 6280 (1.08%) |  |
| number of deaths (all causes)                        | 855               | 892               |  |
| number of deaths resulting from adverse events       | 28                | 18                |  |
| Vascular disorders                                   |                   |                   |  |
| Haematoma  |                   |                   |  |
| subjects affected / exposed                          | 1 / 6359 (0.02%)  | 0 / 6280 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Hypotension  |                   |                   |  |
| subjects affected / exposed                          | 1 / 6359 (0.02%)  | 0 / 6280 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all           | 0 / 1             | 0 / 0             |  |
| General disorders and administration site conditions |                   |                   |  |
| Hypothermia  |                   |                   |  |
| subjects affected / exposed                          | 0 / 6359 (0.00%)  | 1 / 6280 (0.02%)  |  |
| occurrences causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 1             |  |
| Immune system disorders                              |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Allergic reaction                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Pneumothorax                                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 6359 (0.05%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Haemothorax                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 2 / 6280 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary embolism                              |                  |                  |  |
| subjects affected / exposed                     | 3 / 6359 (0.05%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory failure                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 3 / 6280 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute respiratory distress syndrome             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Respiratory arrest                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Pulmonary haemorrhage                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Pulmonary oedema                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychiatric disorders                           |                  |                  |  |
| Psychotic episode                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Investigations                                  |                  |                  |  |
| Abnormal liver function tests                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 6359 (0.03%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Injury, poisoning and procedural complications  |                  |                  |  |
| Fall  |                  |                  |  |
| subjects affected / exposed                     | 4 / 6359 (0.06%) | 3 / 6280 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Traumatic brain injury                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Unintended unilateral bronchial intubation      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute alcoholic intoxication                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye injury                                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hip dislocation                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Overdose  |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac disorders                               |                  |                  |  |
| Atrial fibrillation                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 6359 (0.03%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Supraventricular tachycardia                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac arrest                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 6359 (0.05%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Heart block                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 2 / 6280 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atrial flutter                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bradycardia                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular fibrillation                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Ventricular tachycardia                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nervous system disorders                        |                  |                  |  |
| Cerebral haemorrhage                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 3 / 6280 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Cerebral haematoma                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 6359 (0.03%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epilepsy  |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ischaemic stroke                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 6359 (0.03%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 1 / 2            | 0 / 0            |  |
| Seizure   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Cerebrospinal fluid leakage                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cranial nerve paralysis                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Facial palsy                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hydrocephalus                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stroke  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vasovagal reaction                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventriculitis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Vocal cord paresis                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorders                      |                  |                  |  |
| Ileus   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Constipation                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diarrhoea                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal compartment syndrome                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Bowel obstruction                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Hepatobiliary disorders                         |                  |                  |  |
| Liver failure                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Renal and urinary disorders                     |                  |                  |  |
| Urinary retention                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocrine disorders                             |                  |                  |  |



|   |                   |                   |  |
|---|-------------------|-------------------|--|
| Thyroid haemorrhage                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%)  | 0 / 6280 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Infections and infestations                     |                   |                   |  |
| Pneumonia                                       |                   |                   |  |
| subjects affected / exposed                     | 28 / 6359 (0.44%) | 29 / 6280 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 30            | 0 / 30            |  |
| deaths causally related to treatment / all      | 0 / 7             | 0 / 7             |  |
| Respiratory infection                           |                   |                   |  |
| subjects affected / exposed                     | 6 / 6359 (0.09%)  | 3 / 6280 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urinary tract infection                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%)  | 1 / 6280 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cellulitis                                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%)  | 0 / 6280 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Wound infection                                 |                   |                   |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%)  | 1 / 6280 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Infection MRSA                                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%)  | 1 / 6280 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Meningitis                                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%)  | 2 / 6280 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Clostridium difficile infection                 |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 6359 (0.03%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gangrene  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sepsis  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebrospinal infection                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemophilus influenza pneumonia                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Necrotising fasciitis                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural infection                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Shunt infection                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolism and nutrition disorders              |                  |                  |  |
| Hypokalaemia                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 1 / 6280 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyponatraemia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | Tranexamic acid   | Placebo           |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 84 / 6359 (1.32%) | 72 / 6280 (1.15%) |  |
| Vascular disorders                                    |                   |                   |  |
| Hypertension  |                   |                   |  |
| subjects affected / exposed                           | 0 / 6359 (0.00%)  | 2 / 6280 (0.03%)  |  |
| occurrences (all)                                     | 0                 | 2                 |  |
| Surgical and medical procedures                       |                   |                   |  |
| Fractured zygomatic arch reduction                    |                   |                   |  |
| subjects affected / exposed                           | 0 / 6359 (0.00%)  | 1 / 6280 (0.02%)  |  |
| occurrences (all)                                     | 0                 | 1                 |  |
| Tracheostomy  |                   |                   |  |
| subjects affected / exposed                           | 0 / 6359 (0.00%)  | 1 / 6280 (0.02%)  |  |
| occurrences (all)                                     | 0                 | 1                 |  |
| General disorders and administration site conditions  |                   |                   |  |
| Chest pain  |                   |                   |  |
| subjects affected / exposed                           | 3 / 6359 (0.05%)  | 0 / 6280 (0.00%)  |  |
| occurrences (all)                                     | 3                 | 0                 |  |
| Pyrexia   |                   |                   |  |
| subjects affected / exposed                           | 2 / 6359 (0.03%)  | 2 / 6280 (0.03%)  |  |
| occurrences (all)                                     | 2                 | 2                 |  |
| Immune system disorders                               |                   |                   |  |
| Allergic reaction                                     |                   |                   |  |
| subjects affected / exposed                           | 4 / 6359 (0.06%)  | 4 / 6280 (0.06%)  |  |
| occurrences (all)                                     | 4                 | 4                 |  |
| Respiratory, thoracic and mediastinal                 |                   |                   |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| disorders                                      |                  |                  |  |
| Acute respiratory distress syndrome            |                  |                  |  |
| subjects affected / exposed                    | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences (all)                              | 0                | 1                |  |
| Atelectasis                                    |                  |                  |  |
| subjects affected / exposed                    | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences (all)                              | 0                | 1                |  |
| Haemothorax                                    |                  |                  |  |
| subjects affected / exposed                    | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences (all)                              | 1                | 0                |  |
| Pleural effusion                               |                  |                  |  |
| subjects affected / exposed                    | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences (all)                              | 0                | 1                |  |
| Pneumothorax                                   |                  |                  |  |
| subjects affected / exposed                    | 1 / 6359 (0.02%) | 1 / 6280 (0.02%) |  |
| occurrences (all)                              | 1                | 1                |  |
| Psychiatric disorders                          |                  |                  |  |
| Agitation                                      |                  |                  |  |
| subjects affected / exposed                    | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences (all)                              | 1                | 0                |  |
| Depression                                     |                  |                  |  |
| subjects affected / exposed                    | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences (all)                              | 1                | 0                |  |
| Investigations                                 |                  |                  |  |
| Abnormal liver function tests                  |                  |                  |  |
| subjects affected / exposed                    | 4 / 6359 (0.06%) | 5 / 6280 (0.08%) |  |
| occurrences (all)                              | 4                | 5                |  |
| ECG signs of myocardial ischaemia              |                  |                  |  |
| subjects affected / exposed                    | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences (all)                              | 0                | 1                |  |
| Injury, poisoning and procedural complications |                  |                  |  |
| Fall   |                  |                  |  |
| subjects affected / exposed                    | 5 / 6359 (0.08%) | 2 / 6280 (0.03%) |  |
| occurrences (all)                              | 5                | 2                |  |
| Humerus fracture                               |                  |                  |  |

|  |                       |                       |  |
|--|-----------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all)                                   | 1 / 6359 (0.02%)<br>1 | 0 / 6280 (0.00%)<br>0 |  |
| Laceration of head<br>subjects affected / exposed<br>occurrences (all)             | 1 / 6359 (0.02%)<br>1 | 0 / 6280 (0.00%)<br>0 |  |
| Tracheostomy complication<br>subjects affected / exposed<br>occurrences (all)      | 0 / 6359 (0.00%)<br>0 | 1 / 6280 (0.02%)<br>1 |  |
| Cardiac disorders  |                       |                       |  |
| Atrial flutter<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 6359 (0.05%)<br>3 | 1 / 6280 (0.02%)<br>1 |  |
| Heart block<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 6359 (0.02%)<br>1 | 0 / 6280 (0.00%)<br>0 |  |
| Sinus pause<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 6359 (0.02%)<br>1 | 0 / 6280 (0.00%)<br>0 |  |
| Supraventricular tachycardia<br>subjects affected / exposed<br>occurrences (all)   | 2 / 6359 (0.03%)<br>2 | 2 / 6280 (0.03%)<br>2 |  |
| Nervous system disorders   |                       |                       |  |
| Cranial nerve palsies multiple<br>subjects affected / exposed<br>occurrences (all) | 0 / 6359 (0.00%)<br>0 | 1 / 6280 (0.02%)<br>1 |  |
| Epilepsy<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 6359 (0.00%)<br>0 | 1 / 6280 (0.02%)<br>1 |  |
| Foot drop<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 6359 (0.00%)<br>0 | 1 / 6280 (0.02%)<br>1 |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                       | 5 / 6359 (0.08%)<br>5 | 1 / 6280 (0.02%)<br>1 |  |
| Intracranial venous sinus thrombosis   |                       |                       |  |

|                                      |                  |                  |  |
|--------------------------------------|------------------|------------------|--|
| subjects affected / exposed          | 1 / 6359 (0.02%) | 2 / 6280 (0.03%) |  |
| occurrences (all)                    | 1                | 2                |  |
| Metabolic encephalopathy             |                  |                  |  |
| subjects affected / exposed          | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences (all)                    | 1                | 0                |  |
| Neuroleptic malignant syndrome       |                  |                  |  |
| subjects affected / exposed          | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences (all)                    | 0                | 1                |  |
| Paraesthesia                         |                  |                  |  |
| subjects affected / exposed          | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences (all)                    | 1                | 0                |  |
| Seizure                              |                  |                  |  |
| subjects affected / exposed          | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences (all)                    | 1                | 0                |  |
| Blood and lymphatic system disorders |                  |                  |  |
| Anaemia                              |                  |                  |  |
| subjects affected / exposed          | 0 / 6359 (0.00%) | 2 / 6280 (0.03%) |  |
| occurrences (all)                    | 0                | 2                |  |
| Neutropenia                          |                  |                  |  |
| subjects affected / exposed          | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences (all)                    | 2                | 0                |  |
| Thrombocytopenia                     |                  |                  |  |
| subjects affected / exposed          | 2 / 6359 (0.03%) | 0 / 6280 (0.00%) |  |
| occurrences (all)                    | 2                | 0                |  |
| Thrombocythaemia                     |                  |                  |  |
| subjects affected / exposed          | 0 / 6359 (0.00%) | 1 / 6280 (0.02%) |  |
| occurrences (all)                    | 0                | 1                |  |
| Thrombocytosis                       |                  |                  |  |
| subjects affected / exposed          | 1 / 6359 (0.02%) | 1 / 6280 (0.02%) |  |
| occurrences (all)                    | 1                | 1                |  |
| Eye disorders                        |                  |                  |  |
| Corneal ulcer                        |                  |                  |  |
| subjects affected / exposed          | 1 / 6359 (0.02%) | 0 / 6280 (0.00%) |  |
| occurrences (all)                    | 1                | 0                |  |
| Gastrointestinal disorders           |                  |                  |  |

|  |                       |                       |  |
|--|-----------------------|-----------------------|--|
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 6359 (0.00%)<br>0 | 1 / 6280 (0.02%)<br>1 |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 6359 (0.00%)<br>0 | 2 / 6280 (0.03%)<br>2 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 6359 (0.02%)<br>1 | 0 / 6280 (0.00%)<br>0 |  |
| Ileus<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6359 (0.00%)<br>0 | 2 / 6280 (0.03%)<br>2 |  |
| Intestinal pseudo-obstruction<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 6359 (0.02%)<br>1 | 1 / 6280 (0.02%)<br>1 |  |
| Rectal bleeding<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 6359 (0.02%)<br>1 | 0 / 6280 (0.00%)<br>0 |  |
| Toothache<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 6359 (0.00%)<br>0 | 1 / 6280 (0.02%)<br>1 |  |
| Hepatobiliary disorders<br>Hyperbilirubinaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 6359 (0.02%)<br>1 | 0 / 6280 (0.00%)<br>0 |  |
| Obstructive jaundice<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 6359 (0.00%)<br>0 | 1 / 6280 (0.02%)<br>1 |  |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all) | 1 / 6359 (0.02%)<br>1 | 1 / 6280 (0.02%)<br>1 |  |
| Renal and urinary disorders<br>Haematuria<br>subjects affected / exposed<br>occurrences (all)      | 0 / 6359 (0.00%)<br>0 | 1 / 6280 (0.02%)<br>1 |  |
| Painful urination  |                       |                       |  |

|  |                       |                       |  |
|--|-----------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all)                           | 0 / 6359 (0.00%)<br>0 | 1 / 6280 (0.02%)<br>1 |  |
| Urinary retention<br>subjects affected / exposed<br>occurrences (all)      | 2 / 6359 (0.03%)<br>2 | 1 / 6280 (0.02%)<br>1 |  |
| Musculoskeletal and connective tissue disorders                            |                       |                       |  |
| Cervical pain<br>subjects affected / exposed<br>occurrences (all)          | 0 / 6359 (0.00%)<br>0 | 1 / 6280 (0.02%)<br>1 |  |
| Jaw pain<br>subjects affected / exposed<br>occurrences (all)               | 1 / 6359 (0.02%)<br>1 | 0 / 6280 (0.00%)<br>0 |  |
| Leg pain<br>subjects affected / exposed<br>occurrences (all)               | 0 / 6359 (0.00%)<br>0 | 1 / 6280 (0.02%)<br>1 |  |
| Infections and infestations  |                       |                       |  |
| Bacteraemia<br>subjects affected / exposed<br>occurrences (all)            | 0 / 6359 (0.00%)<br>0 | 1 / 6280 (0.02%)<br>1 |  |
| Cellulitis<br>subjects affected / exposed<br>occurrences (all)             | 3 / 6359 (0.05%)<br>3 | 4 / 6280 (0.06%)<br>4 |  |
| Central line infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 6359 (0.02%)<br>1 | 0 / 6280 (0.00%)<br>0 |  |
| Herpes zoster<br>subjects affected / exposed<br>occurrences (all)          | 1 / 6359 (0.02%)<br>1 | 0 / 6280 (0.00%)<br>0 |  |
| Infection MRSA<br>subjects affected / exposed<br>occurrences (all)         | 1 / 6359 (0.02%)<br>1 | 1 / 6280 (0.02%)<br>1 |  |
| Laryngopharyngitis<br>subjects affected / exposed<br>occurrences (all)     | 1 / 6359 (0.02%)<br>1 | 0 / 6280 (0.00%)<br>0 |  |
| Meningitis   |                       |                       |  |



|   |                         |                         |  |
|---|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 6359 (0.02%)<br>1   | 0 / 6280 (0.00%)<br>0   |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)   | 20 / 6359 (0.31%)<br>21 | 20 / 6280 (0.32%)<br>20 |  |
| Respiratory infection<br>subjects affected / exposed<br>occurrences (all)                                       | 4 / 6359 (0.06%)<br>4   | 4 / 6280 (0.06%)<br>4   |  |
| Sepsis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6359 (0.00%)<br>0   | 1 / 6280 (0.02%)<br>1   |  |
| Tracheostomy infection<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 6359 (0.02%)<br>1   | 0 / 6280 (0.00%)<br>0   |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                     | 8 / 6359 (0.13%)<br>8   | 4 / 6280 (0.06%)<br>4   |  |
| Wound dehiscence<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6359 (0.00%)<br>0   | 2 / 6280 (0.03%)<br>2   |  |
| Wound infection<br>subjects affected / exposed<br>occurrences (all)   | 4 / 6359 (0.06%)<br>4   | 2 / 6280 (0.03%)<br>2   |  |
| Metabolism and nutrition disorders<br>Diabetic ketoacidosis<br>subjects affected / exposed<br>occurrences (all) | 1 / 6359 (0.02%)<br>1   | 0 / 6280 (0.00%)<br>0   |  |
| Hypernatraemia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 6359 (0.02%)<br>1   | 0 / 6280 (0.00%)<br>0   |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 06 September 2016 | <p><b>ELIGIBILITY:</b><br/>Although there was no change to the original eligibility criteria, for the remainder of the trial we limited recruitment to patients who were within 3 hours of injury.</p> <p><b>PRIMARY OUTCOME:</b><br/>The primary outcome included only patients randomised within 3 hours of injury. The primary outcome is death in hospital within 28 days of injury among patients randomised within 3 hours of injury (cause-specific mortality was also recorded).</p> <p><b>SAMPLE SIZE</b><br/>A study with 10,000 traumatic brain injury (TBI) patients randomised within 3 hours of injury would have about 90% power (two sided alpha=1%) to detect a 15% relative reduction (from 20% to 17%) in allcause mortality. About three thousand patients had been recruited beyond three hours of injury already, therefore the total sample size was increased to approximately 13,000 patients.</p> <p><b>STATISTICAL ANALYSIS:</b><br/>We expected tranexamic acid (TXA) to be most effective when given soon after injury, when tissue plasminogen activator (TPA) levels are highest, and less effective when given several hours after injury when the risk of thrombotic DIC may be increased. We planned to examine this hypothesis by conducting a subgroup analysis of the effect of TXA according to the time interval between injury and TXA treatment (<math>\leq 1</math>, <math>&gt; 1</math> to <math>\leq 3</math>, <math>&gt; 3</math> h). The outcome measure for this subgroup analysis was death due to head injury.</p> <p><b>RATIONALE:</b><br/>After the CRASH3 trial had started, new research suggested that TXA was likely to be most effective in the first few hours after injury and less effective when given later. To ensure that the CRASH3 trial was large enough to reliably confirm or refute an early (<math>&lt; 3</math> hours) treatment benefit, the sample size was increased from 10,000 to 13,000 patients with the aim to enrol 10,000 patients within 3 hours of injury. In addition, the primary outcome was been amended to deaths among patients treated within 3 hours of injury.</p> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported