



## Clinical trial results:

### Tranexamic acid for the treatment of gastrointestinal haemorrhage: an international randomised, double blind placebo controlled trial

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-003192-19 |
| Trial protocol           | GB RO ES IE    |
| Global end of trial date | 19 July 2019   |

#### Results information

|                                   |  |
|-----------------------------------|--|
| Result version number             | v1 (current)   |
| This version publication date     | 07 August 2020   |
| First version publication date    | 07 August 2020   |
| Summary attachment (see zip file) | HALT-IT publication (HALT-IT_The Lancet.pdf)<br>HALT-IT The Lancet figures (HALT-IT The Lancet figures.ppt)<br>HALT-IT The Lancet supplementary files (HALT-IT_The Lancet supplementary files.pdf) |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | ISRCTN11225767 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN11225767 |
| ClinicalTrials.gov id (NCT number) | NCT01658124    |
| 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 02079588113, haleema.shakur-still@lshtm.ac.uk |
| Scientific contact           | Ian Roberts, London School Of Hygiene and Tropical Medicine, +44 02079588113, Ian.roberts@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                       | 04 November 2019 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 19 July 2019     |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 19 July 2019     |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The HALT-IT trial will find out whether early administration of tranexamic acid improves outcomes for people who suffered of significant gastrointestinal bleeding. The main outcome is death from haemorrhage within 5 days of randomisation. 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                          | 04 July 2013 |
| 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: 287         |
| Country: Number of subjects enrolled | Spain: 17            |
| Country: Number of subjects enrolled | United Kingdom: 4751 |
| Country: Number of subjects enrolled | Pakistan: 4420       |
| Country: Number of subjects enrolled | Egypt: 709           |
| Country: Number of subjects enrolled | Nigeria: 770         |
| Country: Number of subjects enrolled | Australia: 11        |
| Country: Number of subjects enrolled | Papua New Guinea: 13 |
| Country: Number of subjects enrolled | Malaysia: 464        |
| Country: Number of subjects enrolled | Georgia: 425         |
| Country: Number of subjects enrolled | Nepal: 50            |
| Country: Number of subjects enrolled | Sudan: 40            |
| Country: Number of subjects enrolled | Saudi Arabia: 19     |
| Country: Number of subjects enrolled | Ireland: 17          |
| Country: Number of subjects enrolled | Albania: 16          |

|                                    |       |
|------------------------------------|-------|
| Worldwide total number of subjects | 12009 |
| EEA total number of subjects       | 5072  |

Notes:

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**Subjects enrolled per age group**

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|   |      |
|---|------|
| 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)                     | 1    |
| Adolescents (12-17 years)                 | 6    |
| Adults (18-64 years)                      | 7673 |
| From 65 to 84 years                       | 3491 |
| 85 years and over                         | 838  |

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## Subject disposition

### Recruitment

Recruitment details:

The HALT-IT trial randomised patients aged 16 or older with significant upper or lower gastrointestinal bleeding in 164 hospitals in 15 countries.

The first patient was randomised on 04/07/2013 and the final patient on 21/06/2029.

### Pre-assignment

Screening details:

All adult patients with significant acute upper or lower GI bleeding. The diagnosis of significant bleeding is clinical but significant implies a risk of bleeding to death. The fundamental eligibility criterion is the responsible clinician's 'uncertainty' as to whether or not to use tranexamic acid in a particular patient with GI bleeding.

### 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               | 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 3 g over 24 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 3 g over 24 h.

| <b>Number of subjects in period 1</b>         | Tranexamic acid | Placebo |
|---|-----------------|---------|
| Started                                       | 5994            | 6015    |
| Completed                                     | 5985            | 6004    |
| Not completed                                 | 9               | 11      |
| Consent withdrawn so outcome data unavailable | 6               | 11      |
| Lost to follow-up                             | 3               | -       |

## 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                                     | 5994            | 6015    | 12009 |
| Age categorical<br>Units: Subjects                     |                 |         |       |
| <40 years  | 791             | 779     | 1570  |
| 40-59 years  | 2356            | 2333    | 4689  |
| 60-79 years  | 2078            | 2130    | 4208  |
| ≥80  | 769             | 773     | 1542  |
| Gender categorical<br>Units: Subjects                  |                 |         |       |
| Female   | 2142            | 2124    | 4266  |
| Male   | 3852            | 3891    | 7743  |
| Time from onset to randomisation, h<br>Units: Subjects |                 |         |       |
| ≤3   | 960             | 975     | 1935  |
| >3-≤8  | 1607            | 1551    | 3158  |
| >8   | 3427            | 3488    | 6915  |
| Missing  | 0               | 1       | 1     |
| Suspected location of bleeding<br>Units: Subjects      |                 |         |       |
| Lower  | 674             | 654     | 1328  |
| Upper  | 5320            | 5361    | 10681 |
| Hematemesis<br>Units: Subjects                         |                 |         |       |
| Yes  | 4285            | 4240    | 8525  |
| No   | 1709            | 1775    | 3484  |
| Melaena or fresh blood per rectum<br>Units: Subjects   |                 |         |       |
| Yes  | 4573            | 4626    | 9199  |
| No   | 1421            | 1389    | 2810  |
| Suspected variceal bleeding<br>Units: Subjects         |                 |         |       |
| Yes  | 2694            | 2739    | 5433  |
| No   | 3300            | 3276    | 6576  |
| Suspected active bleeding<br>Units: Subjects           |                 |         |       |
| Yes  | 5247            | 5226    | 10473 |
| No   | 747             | 789     | 1536  |
| Systolic blood pressure, mm Hg<br>Units: Subjects      |                 |         |       |

|   |      |      |       |
|---|------|------|-------|
| ≥90   | 5222 | 5216 | 10438 |
| 76-89   | 577  | 577  | 1154  |
| ≤75   | 181  | 201  | 382   |
| Missing   | 14   | 21   | 35    |
| Heart rate, beats per min<br>Units: Subjects  |      |      |       |
| <77   | 812  | 756  | 1568  |
| 77-91   | 1546 | 1644 | 3190  |
| 92-107  | 1760 | 1720 | 3480  |
| >107  | 1864 | 1885 | 3749  |
| Missing   | 12   | 10   | 22    |
| Signs of shock<br>Units: Subjects   |      |      |       |
| Yes   | 2574 | 2648 | 5222  |
| No  | 3420 | 3367 | 6787  |
| Rockall score<br>Units: Subjects  |      |      |       |
| 1-2   | 1419 | 1395 | 2814  |
| 3-4   | 2306 | 2332 | 4638  |
| 5-7   | 2269 | 2288 | 4557  |
| Taking anticoagulants<br>Units: Subjects  |      |      |       |
| Yes   | 528  | 500  | 1028  |
| No  | 5422 | 5466 | 10888 |
| Unknown   | 44   | 49   | 93    |
| Emergency admission<br>Units: Subjects  |      |      |       |
| Yes   | 5673 | 5687 | 11360 |
| No  | 321  | 328  | 649   |
| Major comorbidities   |      |      |       |
| Major co-morbidities are: Cardiovascular (TXA: 1108, Placebo: 1132); Respiratory (TXA: 337, Placebo: 324); Liver (TXA: 2432, Placebo: 2532); Renal (TXA: 325, Placebo: 310); Malignancy (TXA: 417, Placebo: 382); Other (TXA: 999, Placebo: 968). |      |      |       |
| Units: Subjects   |      |      |       |
| Any co-morbidity  | 4308 | 4329 | 8637  |
| No co-morbidity   | 1686 | 1686 | 3372  |

## 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 death due to bleeding within 5 days of randomisation

|                                |   |
|--------------------------------|---|
| End point title                | Effect of tranexamic acid on death due to bleeding within 5 days of randomisation |
| End point description:         |   |
| End point type                 | Primary   |
| End point timeframe:           |   |
| Within 5 days of randomisation |   |

| End point values            | Tranexamic acid | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 5956            | 5981            |  |  |
| Units: Patients             | 222             | 226             |  |  |

|                                   |  |
|-----------------------------------|--|
| <b>Attachments (see zip file)</b> | HALT-IT Primary analysis/HALT-IT primary analysis.pptx |
|-----------------------------------|--|

### Statistical analyses

|   |                           |
|---|---------------------------|
| <b>Statistical analysis title</b>   | Primary analysis          |
| Statistical analysis description:   |                           |
| The primary analyses compared those allocated to tranexamic acid with those allocated to placebo on a modified intention to treat basis, excluding patients who received neither dose of the allocated treatment and those for whom outcome data on death were unavailable. |                           |
| Comparison groups   | Placebo v Tranexamic acid |
| Number of subjects included in analysis   | 11937                     |
| Analysis specification  | Pre-specified             |
| Analysis type   | superiority               |
| Parameter estimate  | Risk ratio (RR)           |
| Point estimate  | 0.99                      |
| Confidence interval   |                           |
| level   | 95 %                      |
| sides   | 2-sided                   |
| lower limit   | 0.82                      |
| upper limit   | 1.18                      |



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**Secondary: Complications-Any Thrombotic event**

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|                 |                                    |
|-----------------|------------------------------------|
| End point title | Complications-Any Thrombotic event |
|-----------------|------------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Within 28 days of randomisation

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| End point values            | Tranexamic acid | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 5952            | 5977            |  |  |
| Units: Any Thrombotic event | 86              | 72              |  |  |

**Statistical analyses**

|                                   |                                    |
|-----------------------------------|------------------------------------|
| <b>Statistical analysis title</b> | Complications-Any thrombotic event |
|-----------------------------------|------------------------------------|

|                   |                           |
|-------------------|---------------------------|
| Comparison groups | Tranexamic acid v Placebo |
|-------------------|---------------------------|

|   |       |
|---|-------|
| Number of subjects included in analysis | 11929 |
|---|-------|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |             |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

|                    |                 |
|--------------------|-----------------|
| Parameter estimate | Risk ratio (RR) |
|--------------------|-----------------|

|                |     |
|----------------|-----|
| Point estimate | 1.2 |
|----------------|-----|

Confidence interval

|       |      |
|-------|------|
| level | 95 % |
|-------|------|

|       |         |
|-------|---------|
| sides | 2-sided |
|-------|---------|

|             |      |
|-------------|------|
| lower limit | 0.88 |
|-------------|------|

|             |      |
|-------------|------|
| upper limit | 1.64 |
|-------------|------|

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**Secondary: Complications-Venous events**

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|                 |                             |
|-----------------|-----------------------------|
| End point title | Complications-Venous events |
|-----------------|-----------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Within 28 days of randomisation

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|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | Tranexamic acid | Placebo         |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 5952            | 5977            |  |  |
| Units: Venous events        | 48              | 26              |  |  |

## Statistical analyses

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | Complications- Venous events |
| Comparison groups                       | Tranexamic acid v Placebo    |
| Number of subjects included in analysis | 11929                        |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| Parameter estimate                      | Risk ratio (RR)              |
| Point estimate                          | 1.85                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 1.15                         |
| upper limit                             | 2.98                         |

## Secondary: Complications- Deep vein thrombosis

|                                 |                                     |
|---------------------------------|-------------------------------------|
| End point title                 | Complications- Deep vein thrombosis |
| End point description:          |                                     |
| End point type                  | Secondary                           |
| End point timeframe:            |                                     |
| Within 28 days of randomisation |                                     |

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | Tranexamic acid | Placebo         |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 5952            | 5977            |  |  |
| Units: Deep vein thrombosis | 23              | 12              |  |  |

## Statistical analyses

|                                   |                                    |
|-----------------------------------|------------------------------------|
| <b>Statistical analysis title</b> | Complications Deep Vein Thrombosis |
| Comparison groups                 | Tranexamic acid v Placebo          |

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 11929           |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority     |
| Parameter estimate                      | Risk ratio (RR) |
| Point estimate                          | 1.92            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.96            |
| upper limit                             | 3.86            |

### Secondary: Complications- Pulmonary embolism

|                                 |                                   |
|---------------------------------|-----------------------------------|
| End point title                 | Complications- Pulmonary embolism |
| End point description:          |                                   |
| End point type                  | Secondary                         |
| 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 | 5952            | 5977            |  |  |
| Units: Pulmonary embolism   | 28              | 16              |  |  |

### Statistical analyses

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>       | Complications-Pulmonary embolism |
| Comparison groups                       | Tranexamic acid v Placebo        |
| Number of subjects included in analysis | 11929                            |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| Parameter estimate                      | Risk ratio (RR)                  |
| Point estimate                          | 1.76                             |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 0.95                             |
| upper limit                             | 3.24                             |

### Secondary: Complications-Arterial events

|                                 |                               |
|---------------------------------|-------------------------------|
| End point title                 | Complications-Arterial events |
| End point description:          |                               |
| End point type                  | Secondary                     |
| 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 | 5952            | 5977            |  |  |
| Units: Arterial events      | 42              | 46              |  |  |

### Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Complications- Arterial events |
| Comparison groups                       | Tranexamic acid v Placebo      |
| Number of subjects included in analysis | 11929                          |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| Parameter estimate                      | Risk ratio (RR)                |
| Point estimate                          | 0.92                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.6                            |
| upper limit                             | 1.39                           |

### Secondary: Complications- Myocardial infarction

|                                 |                                      |
|---------------------------------|--------------------------------------|
| End point title                 | Complications- Myocardial infarction |
| End point description:          |                                      |
| End point type                  | Secondary                            |
| 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  | 5952            | 5977            |  |  |
| Units: Myocardial infarction | 24              | 28              |  |  |

## Statistical analyses

| Statistical analysis title              | Complications- Myocardial infarction |
|---|--------------------------------------|
| Comparison groups                       | Tranexamic acid v Placebo            |
| Number of subjects included in analysis | 11929                                |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | superiority                          |
| Parameter estimate                      | Risk ratio (RR)                      |
| Point estimate                          | 0.86                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | 0.5                                  |
| upper limit                             | 1.48                                 |

## Secondary: Complications- Stroke

|                                 |                       |
|---------------------------------|-----------------------|
| End point title                 | Complications- Stroke |
| End point description:          |                       |
| End point type                  | Secondary             |
| 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 | 5952            | 5977            |  |  |
| Units: Stroke               | 19              | 18              |  |  |

## Statistical analyses

| Statistical analysis title | Complications- Stroke     |
|----------------------------|---------------------------|
| Comparison groups          | Tranexamic acid v Placebo |

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 11929           |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority     |
| Parameter estimate                      | Risk ratio (RR) |
| Point estimate                          | 1.06            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.56            |
| upper limit                             | 2.02            |

### Secondary: Complications-Renal failure

|                                 |                             |
|---------------------------------|-----------------------------|
| End point title                 | Complications-Renal failure |
| End point description:          |                             |
| End point type                  | Secondary                   |
| 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 | 5951            | 5978            |  |  |
| Units: Renal failure        | 142             | 157             |  |  |

### Statistical analyses

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Complications-Renal failure |
| Comparison groups                       | Tranexamic acid v Placebo   |
| Number of subjects included in analysis | 11929                       |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| Parameter estimate                      | Risk ratio (RR)             |
| Point estimate                          | 0.91                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.73                        |
| upper limit                             | 1.14                        |

### Secondary: Complications-Liver failure

|                                 |                             |
|---------------------------------|-----------------------------|
| End point title                 | Complications-Liver failure |
| End point description:          |                             |
| End point type                  | Secondary                   |
| 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 | 5952            | 5977            |  |  |
| Units: Liver failure        | 196             | 184             |  |  |

### Statistical analyses

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | Complications- Liver failure |
| Comparison groups                       | Tranexamic acid v Placebo    |
| Number of subjects included in analysis | 11929                        |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| Parameter estimate                      | Risk ratio (RR)              |
| Point estimate                          | 1.07                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.88                         |
| upper limit                             | 1.3                          |

### Secondary: Complications- Respiratory failure

|                                 |                                    |
|---------------------------------|------------------------------------|
| End point title                 | Complications- Respiratory failure |
| End point description:          |                                    |
| End point type                  | Secondary                          |
| End point timeframe:            |                                    |
| Within 28 days of randomisation |                                    |

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | Tranexamic acid | Placebo         |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 5952            | 5978            |  |  |
| Units: Respiratory failure  | 105             | 131             |  |  |

### Statistical analyses

|   |                                    |
|---|------------------------------------|
| <b>Statistical analysis title</b>       | Complications -Respiratory failure |
| Comparison groups                       | Tranexamic acid v Placebo          |
| Number of subjects included in analysis | 11930                              |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | superiority                        |
| Parameter estimate                      | Risk ratio (RR)                    |
| Point estimate                          | 0.81                               |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | 0.62                               |
| upper limit                             | 1.04                               |

### Secondary: Complications- Cardiac event

|                                 |                              |
|---------------------------------|------------------------------|
| End point title                 | Complications- Cardiac event |
| End point description:          |                              |
| End point type                  | Secondary                    |
| End point timeframe:            |                              |
| Within 28 days of randomisation |                              |

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | Tranexamic acid | Placebo         |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 5952            | 5977            |  |  |
| Units: Cardiac event        | 100             | 89              |  |  |

### Statistical analyses

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | Complications- Cardiac event |
| Comparison groups                 | Tranexamic acid v Placebo    |



|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 11929           |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority     |
| Parameter estimate                      | Risk ratio (RR) |
| Point estimate                          | 1.13            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.85            |
| upper limit                             | 1.5             |

### Secondary: Complications- Sepsis

|                                 |                       |
|---------------------------------|-----------------------|
| End point title                 | Complications- Sepsis |
| End point description:          |                       |
| End point type                  | Secondary             |
| End point timeframe:            |                       |
| Within 28 days of ransomisation |                       |

| End point values            | Tranexamic acid | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 5952            | 5977            |  |  |
| Units: Sepsis               | 210             | 216             |  |  |

### Statistical analyses

|   |                           |
|---|---------------------------|
| <b>Statistical analysis title</b>       | Complications- Sepsis     |
| Comparison groups                       | Tranexamic acid v Placebo |
| Number of subjects included in analysis | 11929                     |
| Analysis specification                  | Pre-specified             |
| Analysis type                           |                           |
| Parameter estimate                      | Risk ratio (RR)           |
| Point estimate                          | 0.98                      |
| Confidence interval                     |                           |
| level                                   | 95 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | 0.81                      |
| upper limit                             | 1.18                      |

### Secondary: Complications- Pneumonia

|                                 |                          |
|---------------------------------|--------------------------|
| End point title                 | Complications- Pneumonia |
| End point description:          |                          |
| End point type                  | Secondary                |
| 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 | 5952            | 5978            |  |  |
| Units: Pneumonia            | 193             | 174             |  |  |

### Statistical analyses

|   |                           |
|---|---------------------------|
| <b>Statistical analysis title</b>       | Complications-Pneumonia   |
| Comparison groups                       | Tranexamic acid v Placebo |
| Number of subjects included in analysis | 11930                     |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | superiority               |
| Parameter estimate                      | Risk ratio (RR)           |
| Point estimate                          | 1.11                      |
| Confidence interval                     |                           |
| level                                   | 95 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | 0.91                      |
| upper limit                             | 1.36                      |

### Secondary: Complications- Seizure

|                                 |                        |
|---------------------------------|------------------------|
| End point title                 | Complications- Seizure |
| End point description:          |                        |
| End point type                  | Secondary              |
| End point timeframe:            |                        |
| Within 28 days of randomisation |                        |

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | Tranexamic acid | Placebo         |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 5952            | 5977            |  |  |
| Units: Seizure              | 38              | 22              |  |  |

## Statistical analyses

|   |                           |
|---|---------------------------|
| <b>Statistical analysis title</b>       | Complications- Seizure    |
| Comparison groups                       | Tranexamic acid v Placebo |
| Number of subjects included in analysis | 11929                     |
| Analysis specification                  | Pre-specified             |
| Analysis type                           |                           |
| Parameter estimate                      | Risk ratio (RR)           |
| Point estimate                          | 1.73                      |
| Confidence interval                     |                           |
| level                                   | 95 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | 1.03                      |
| upper limit                             | 2.93                      |

## 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 | 16.0 |
|--------------------|------|

### 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   | 173 / 5985 (2.89%) | 186 / 6004 (3.10%) |  |
| number of deaths (all causes)                                       | 564                | 548                |  |
| number of deaths resulting from adverse events                      |                    |                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |  |
| Adenocarcinoma  |                    |                    |  |
| subjects affected / exposed   | 0 / 5985 (0.00%)   | 1 / 6004 (0.02%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0              | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 1              |  |
| Cholangiocarcinoma  |                    |                    |  |
| subjects affected / exposed   | 0 / 5985 (0.00%)   | 1 / 6004 (0.02%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0              | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 1              |  |
| Colorectal cancer   |                    |                    |  |
| subjects affected / exposed   | 0 / 5985 (0.00%)   | 1 / 6004 (0.02%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0              | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 1              |  |
| Gastric cancer  |                    |                    |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Hepatic cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Hepatocellular carcinoma                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Lung neoplasm malignant                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Meningioma                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal carcinoma                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Vascular disorders                              |                  |                  |  |
| Angiodysplasia                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortic aneurysm rupture                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arterioenteric fistula                          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Deep vein thrombosis                            |                  |                  |  |
| subjects affected / exposed                     | 4 / 5985 (0.07%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Haematoma                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (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 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Orthostatic hypotension                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 2 / 6004 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral embolism                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral ischaemia                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Thrombosis                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Surgical and medical procedures                 |                  |                  |  |
| Chemotherapy                                    |                  |                  |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                          | 0 / 5985 (0.00%) | 3 / 6004 (0.05%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Colectomy  |                  |                  |  |
| subjects affected / exposed                          | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| General disorders and administration site conditions |                  |                  |  |
| Chest pain   |                  |                  |  |
| subjects affected / exposed                          | 1 / 5985 (0.02%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Asthenia   |                  |                  |  |
| subjects affected / exposed                          | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Multi-organ failure                                  |                  |                  |  |
| subjects affected / exposed                          | 2 / 5985 (0.03%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 2            | 0 / 0            |  |
| Oedema   |                  |                  |  |
| subjects affected / exposed                          | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Pyrexia  |                  |                  |  |
| subjects affected / exposed                          | 1 / 5985 (0.02%) | 2 / 6004 (0.03%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Immune system disorders                              |                  |                  |  |
| Hypersensitivity                                     |                  |                  |  |
| subjects affected / exposed                          | 2 / 5985 (0.03%) | 2 / 6004 (0.03%) |  |
| occurrences causally related to treatment / all      | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Aspiration                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic obstructive pulmonary disease           |                  |                  |  |
| subjects affected / exposed                     | 3 / 5985 (0.05%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Dyspnoea  |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pleural effusion                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 2 / 6004 (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 / 5985 (0.05%) | 3 / 6004 (0.05%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Pulmonary oedema                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychiatric disorders                           |                  |                  |  |
| Alcohol withdrawal syndrome                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Confusional state                               |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 5985 (0.03%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Suicidal ideation                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Investigations                                  |                  |                  |  |
| International normalised ratio abnormal         |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury, poisoning and procedural complications  |                  |                  |  |
| Fall  |                  |                  |  |
| subjects affected / exposed                     | 6 / 5985 (0.10%) | 4 / 6004 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Feeding tube complication                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femoral neck fracture                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Overdose  |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural haemorrhage                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Cardiac disorders                               |                  |                  |  |
| Atrial fibrillation                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 2 / 6004 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Cardiac arrest                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Cardiac failure congestive                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 3 / 6004 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Myocardial ischaemia                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Myocardial infarction                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 5985 (0.03%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pericardial effusion                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Supraventricular tachycardia                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular tachycardia                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nervous system disorders                        |                  |                  |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| Central nervous system lesion<br>subjects affected / exposed | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0            | 0 / 1            |  |
| deaths causally related to<br>treatment / all                | 0 / 0            | 0 / 1            |  |
| Cerebral infarction<br>subjects affected / exposed           | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 1            | 0 / 0            |  |
| deaths causally related to<br>treatment / all                | 0 / 1            | 0 / 0            |  |
| Encephalopathy<br>subjects affected / exposed                | 2 / 5985 (0.03%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 2            | 0 / 1            |  |
| deaths causally related to<br>treatment / all                | 0 / 0            | 0 / 0            |  |
| Hepatic encephalopathy<br>subjects affected / exposed        | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0            | 0 / 1            |  |
| deaths causally related to<br>treatment / all                | 0 / 0            | 0 / 0            |  |
| Ischaemic stroke<br>subjects affected / exposed              | 3 / 5985 (0.05%) | 3 / 6004 (0.05%) |  |
| occurrences causally related to<br>treatment / all           | 3 / 3            | 0 / 3            |  |
| deaths causally related to<br>treatment / all                | 0 / 0            | 0 / 1            |  |
| Syncope<br>subjects affected / exposed                       | 1 / 5985 (0.02%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 1            | 0 / 1            |  |
| deaths causally related to<br>treatment / all                | 0 / 0            | 0 / 0            |  |
| Transient ischaemic attack<br>subjects affected / exposed    | 1 / 5985 (0.02%) | 2 / 6004 (0.03%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 1            | 0 / 2            |  |
| deaths causally related to<br>treatment / all                | 0 / 0            | 0 / 0            |  |
| Delirium<br>subjects affected / exposed                      | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to<br>treatment / all           | 0 / 0            | 0 / 1            |  |
| deaths causally related to<br>treatment / all                | 0 / 0            | 0 / 0            |  |
| Blood and lymphatic system disorders                         |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| Anaemia   |                  |                   |  |
| subjects affected / exposed                     | 5 / 5985 (0.08%) | 10 / 6004 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Thrombocytopenia                                |                  |                   |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0             |  |
| Febrile neutropenia                             |                  |                   |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Angina pectoris                                 |                  |                   |  |
| subjects affected / exposed                     | 2 / 5985 (0.03%) | 0 / 6004 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0             |  |
| Ear and labyrinth disorders                     |                  |                   |  |
| Mastoid effusion                                |                  |                   |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Gastrointestinal disorders                      |                  |                   |  |
| Abdominal distension                            |                  |                   |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Abdominal pain                                  |                  |                   |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 2 / 6004 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Enterocolitis                                   |                  |                   |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Ascites   |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal infarction                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal perforation                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Constipation                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 5985 (0.03%) | 2 / 6004 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Crohn's disease                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diarrhoea                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 5985 (0.03%) | 2 / 6004 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum                                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 5985 (0.05%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal perforation                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dyspepsia                                       |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 5985 (0.00%)  | 1 / 6004 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Enterocutaneous fistula                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%)  | 0 / 6004 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Gastric ulcer                                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%)  | 0 / 6004 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastritis                                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%)  | 3 / 6004 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastrointestinal haemorrhage                    |                   |                   |  |
| subjects affected / exposed                     | 59 / 5985 (0.99%) | 74 / 6004 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 64            | 0 / 78            |  |
| deaths causally related to treatment / all      | 0 / 13            | 0 / 9             |  |
| Haemorrhoids                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%)  | 1 / 6004 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Mallory Weiss syndrome                          |                   |                   |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%)  | 1 / 6004 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Oesophagitis                                    |                   |                   |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%)  | 3 / 6004 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Large bowel obstruction                         |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (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 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Perforated gastric ulcer                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Small bowel obstruction                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 5985 (0.03%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Upper gastrointestinal haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vomiting  |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatobiliary disorders                         |                  |                  |  |
| Cholelithiasis                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangitis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gallbladder polyp                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic cirrhosis                               |                  |                  |  |
| subjects affected / exposed                     | 7 / 5985 (0.12%) | 3 / 6004 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 1            |  |
| Hepatitis                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatorenal syndrome                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Ischaemic hepatitis                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Jaundice  |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Jaundice cholestatic                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Portal vein thrombosis                          |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal and urinary disorders                     |                  |                  |  |
| Renal failure                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 5985 (0.03%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Urinary incontinence                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |
| Abscess   |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendicitis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cellulitis                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 5985 (0.03%) | 3 / 6004 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clostridium difficile infection                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 3 / 6004 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Gastroenteritis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infected skin ulcer                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Liver abscess                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower respiratory tract infection               |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritonitis                                     |                  |                  |  |
| subjects affected / exposed                     | 3 / 5985 (0.05%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Pneumonia                                       |                  |                  |  |
| subjects affected / exposed                     | 7 / 5985 (0.12%) | 3 / 6004 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 5            | 0 / 3            |  |
| Pyelonephritis                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Respiratory tract infection                     |                  |                  |  |
| subjects affected / exposed                     | 9 / 5985 (0.15%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sepsis  |                  |                  |  |
| subjects affected / exposed                     | 5 / 5985 (0.08%) | 7 / 6004 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 3            |  |
| Urinary tract infection                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 8 / 5985 (0.13%) | 3 / 6004 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes zoster                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolism and nutrition disorders              |                  |                  |  |
| Dehydration                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fluid overload                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gout  |                  |                  |  |
| subjects affected / exposed                     | 2 / 5985 (0.03%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoglycaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 2 / 6004 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypomagnesaemia                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyponatraemia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 1 / 6004 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Type 2 diabetes mellitus                        |                  |                  |  |

|   |                  |                  |
|---|------------------|------------------|
| subjects affected / exposed                     | 1 / 5985 (0.02%) | 0 / 6004 (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: 0 %

| <b>Non-serious adverse events</b>                     | Tranexamic acid   | Placebo           |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 53 / 5985 (0.89%) | 66 / 6004 (1.10%) |  |
| Vascular disorders                                    |                   |                   |  |
| Haematoma   |                   |                   |  |
| subjects affected / exposed                           | 1 / 5985 (0.02%)  | 0 / 6004 (0.00%)  |  |
| occurrences (all)                                     | 1                 | 0                 |  |
| Hypotension   |                   |                   |  |
| subjects affected / exposed                           | 1 / 5985 (0.02%)  | 0 / 6004 (0.00%)  |  |
| occurrences (all)                                     | 1                 | 0                 |  |
| Phlebitis   |                   |                   |  |
| subjects affected / exposed                           | 2 / 5985 (0.03%)  | 0 / 6004 (0.00%)  |  |
| occurrences (all)                                     | 2                 | 0                 |  |
| Thrombosis  |                   |                   |  |
| subjects affected / exposed                           | 1 / 5985 (0.02%)  | 1 / 6004 (0.02%)  |  |
| occurrences (all)                                     | 1                 | 1                 |  |
| Venous insufficiency                                  |                   |                   |  |
| subjects affected / exposed                           | 0 / 5985 (0.00%)  | 1 / 6004 (0.02%)  |  |
| occurrences (all)                                     | 0                 | 1                 |  |
| General disorders and administration site conditions  |                   |                   |  |
| Chest pain  |                   |                   |  |
| subjects affected / exposed                           | 1 / 5985 (0.02%)  | 1 / 6004 (0.02%)  |  |
| occurrences (all)                                     | 1                 | 1                 |  |
| Oedema  |                   |                   |  |
| subjects affected / exposed                           | 1 / 5985 (0.02%)  | 2 / 6004 (0.03%)  |  |
| occurrences (all)                                     | 1                 | 2                 |  |
| Pain  |                   |                   |  |
| subjects affected / exposed                           | 1 / 5985 (0.02%)  | 0 / 6004 (0.00%)  |  |
| occurrences (all)                                     | 1                 | 0                 |  |
| Pyrexia   |                   |                   |  |

|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed<br>occurrences (all)  | 2 / 5985 (0.03%)<br>2  | 1 / 6004 (0.02%)<br>1  |  |
| Immune system disorders<br>Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)   | 3 / 5985 (0.05%)<br>3  | 4 / 6004 (0.07%)<br>4  |  |
| Respiratory, thoracic and mediastinal disorders<br>Chronic obstructive pulmonary disease<br>subjects affected / exposed<br>occurrences (all)<br><br>Epistaxis<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypoxia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5985 (0.00%)<br>0<br><br>1 / 5985 (0.02%)<br>1<br><br>0 / 5985 (0.00%)<br>0                              | 1 / 6004 (0.02%)<br>1<br><br>1 / 6004 (0.02%)<br>1<br><br>1 / 6004 (0.02%)<br>1                              |  |
| Psychiatric disorders<br>Alcohol withdrawal syndrome<br>subjects affected / exposed<br>occurrences (all)<br><br>Confusional state<br>subjects affected / exposed<br>occurrences (all)<br><br>Delirium<br>subjects affected / exposed<br>occurrences (all)<br><br>Panic attack<br>subjects affected / exposed<br>occurrences (all) | 0 / 5985 (0.00%)<br>0<br><br>1 / 5985 (0.02%)<br>1<br><br>1 / 5985 (0.02%)<br>1<br><br>1 / 5985 (0.02%)<br>1 | 2 / 6004 (0.03%)<br>2<br><br>0 / 6004 (0.00%)<br>0<br><br>1 / 6004 (0.02%)<br>1<br><br>0 / 6004 (0.00%)<br>0 |  |
| Injury, poisoning and procedural complications<br>Alcohol poisoning<br>subjects affected / exposed<br>occurrences (all)<br><br>Contusion  | 1 / 5985 (0.02%)<br>1  | 0 / 6004 (0.00%)<br>0  |  |

|   |                       |                       |  |
|---|-----------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 5985 (0.02%)<br>1 | 0 / 6004 (0.00%)<br>0 |  |
| Fall<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5985 (0.00%)<br>0 | 4 / 6004 (0.07%)<br>5 |  |
| Gastrointestinal stoma complication<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |
| Haematuria traumatic<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |
| Haemodilution<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5985 (0.02%)<br>1 | 0 / 6004 (0.00%)<br>0 |  |
| Head injury<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5985 (0.02%)<br>1 | 0 / 6004 (0.00%)<br>0 |  |
| Humerus fracture<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |
| Overdose<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |
| Transfusion reaction<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |
| Congenital, familial and genetic disorders<br>Hydrocele<br>subjects affected / exposed<br>occurrences (all)             | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |
| Cardiac disorders<br>Cardiac failure<br>subjects affected / exposed<br>occurrences (all)<br><br>Cardiovascular disorder | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |

|   |                       |                       |  |
|---|-----------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 5985 (0.00%)<br>0 | 2 / 6004 (0.03%)<br>2 |  |
| Cyanosis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 5985 (0.02%)<br>1 | 0 / 6004 (0.00%)<br>0 |  |
| Nervous system disorders<br>Seizure<br>subjects affected / exposed<br>occurrences (all)             | 2 / 5985 (0.03%)<br>3 | 1 / 6004 (0.02%)<br>1 |  |
| Encephalopathy<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 5985 (0.00%)<br>0 | 2 / 6004 (0.03%)<br>2 |  |
| Coagulopathy<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 5985 (0.02%)<br>1 | 0 / 6004 (0.00%)<br>0 |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |
| Eye disorders<br>Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 5985 (0.02%)<br>1 | 0 / 6004 (0.00%)<br>0 |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)    | 1 / 5985 (0.02%)<br>1 | 1 / 6004 (0.02%)<br>1 |  |
| Ascites   |                       |                       |  |

|   |                       |                       |  |
|---|-----------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 5985 (0.00%)<br>0 | 3 / 6004 (0.05%)<br>3 |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)  | 3 / 5985 (0.05%)<br>3 | 1 / 6004 (0.02%)<br>1 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5985 (0.02%)<br>1 | 0 / 6004 (0.00%)<br>0 |  |
| Gastritis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |
| Gastrointestinal haemorrhage<br>subjects affected / exposed<br>occurrences (all)                              | 2 / 5985 (0.03%)<br>2 | 2 / 6004 (0.03%)<br>2 |  |
| Haemorrhoids<br>subjects affected / exposed<br>occurrences (all)  | 1 / 5985 (0.02%)<br>1 | 1 / 6004 (0.02%)<br>1 |  |
| Lip swelling<br>subjects affected / exposed<br>occurrences (all)  | 1 / 5985 (0.02%)<br>1 | 0 / 6004 (0.00%)<br>0 |  |
| Small intestinal obstruction<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |
| Hepatobiliary disorders<br>Portal vein thrombosis<br>subjects affected / exposed<br>occurrences (all)         | 1 / 5985 (0.02%)<br>1 | 0 / 6004 (0.00%)<br>0 |  |
| Skin and subcutaneous tissue disorders<br>Decubitus ulcer<br>subjects affected / exposed<br>occurrences (all) | 1 / 5985 (0.02%)<br>1 | 1 / 6004 (0.02%)<br>1 |  |
| Erythema  |                       |                       |  |



|  |                       |                       |  |
|--|-----------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 5985 (0.02%)<br>1 | 1 / 6004 (0.02%)<br>1 |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5985 (0.02%)<br>1 | 0 / 6004 (0.00%)<br>0 |  |
| Renal and urinary disorders<br>Urinary retention<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 5985 (0.02%)<br>1 | 1 / 6004 (0.02%)<br>1 |  |
| Musculoskeletal and connective tissue disorders<br>Crystal arthropathy<br>subjects affected / exposed<br>occurrences (all) | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |
| Groin pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5985 (0.02%)<br>1 | 0 / 6004 (0.00%)<br>0 |  |
| Infections and infestations<br>Abscess<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |
| Cellulitis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5985 (0.02%)<br>1 | 1 / 6004 (0.02%)<br>1 |  |
| Clostridium difficile infection<br>subjects affected / exposed<br>occurrences (all)  | 1 / 5985 (0.02%)<br>1 | 3 / 6004 (0.05%)<br>3 |  |
| Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 5985 (0.02%)<br>1 | 0 / 6004 (0.00%)<br>0 |  |
| Oesophageal candidiasis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5985 (0.00%)<br>0 | 3 / 6004 (0.05%)<br>3 |  |
| Otitis externa<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5985 (0.00%)<br>0 | 1 / 6004 (0.02%)<br>1 |  |
| Peritonitis  |                       |                       |  |

|                                    |                  |                  |  |
|------------------------------------|------------------|------------------|--|
| subjects affected / exposed        | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences (all)                  | 1                | 0                |  |
| Pharyngitis                        |                  |                  |  |
| subjects affected / exposed        | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences (all)                  | 1                | 0                |  |
| Pneumonia                          |                  |                  |  |
| subjects affected / exposed        | 2 / 5985 (0.03%) | 0 / 6004 (0.00%) |  |
| occurrences (all)                  | 2                | 0                |  |
| Respiratory tract infection        |                  |                  |  |
| subjects affected / exposed        | 3 / 5985 (0.05%) | 1 / 6004 (0.02%) |  |
| occurrences (all)                  | 3                | 1                |  |
| Sepsis                             |                  |                  |  |
| subjects affected / exposed        | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences (all)                  | 1                | 0                |  |
| Staphylococcal bacteraemia         |                  |                  |  |
| subjects affected / exposed        | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences (all)                  | 1                | 0                |  |
| Urinary tract infection            |                  |                  |  |
| subjects affected / exposed        | 4 / 5985 (0.07%) | 9 / 6004 (0.15%) |  |
| occurrences (all)                  | 4                | 9                |  |
| Metabolism and nutrition disorders |                  |                  |  |
| Fluid overload                     |                  |                  |  |
| subjects affected / exposed        | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences (all)                  | 1                | 0                |  |
| Fluid retention                    |                  |                  |  |
| subjects affected / exposed        | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences (all)                  | 1                | 0                |  |
| Gout                               |                  |                  |  |
| subjects affected / exposed        | 1 / 5985 (0.02%) | 1 / 6004 (0.02%) |  |
| occurrences (all)                  | 1                | 1                |  |
| Hypernatraemia                     |                  |                  |  |
| subjects affected / exposed        | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences (all)                  | 0                | 1                |  |
| Hypoglycaemia                      |                  |                  |  |
| subjects affected / exposed        | 1 / 5985 (0.02%) | 0 / 6004 (0.00%) |  |
| occurrences (all)                  | 1                | 0                |  |

|                             |                  |                  |  |
|-----------------------------|------------------|------------------|--|
| Hypokalaemia                |                  |                  |  |
| subjects affected / exposed | 1 / 5985 (0.02%) | 1 / 6004 (0.02%) |  |
| occurrences (all)           | 2                | 1                |  |
| Hyponatraemia               |                  |                  |  |
| subjects affected / exposed | 0 / 5985 (0.00%) | 1 / 6004 (0.02%) |  |
| occurrences (all)           | 0                | 1                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 14 November 2017 | <p>Trial design: The sample size was increased from 8,000 to 12,000 patients<br/>Planned date of last patient enrolment: was changed from 30 November 2017 to 31 May 2019<br/>Secondary outcomes: Death from haemorrhage was added as secondary outcome.<br/>Administration of treatment: The sentence "Where fluid restriction is needed the volume used to administer the maintenance dose can be reduced to 500 mL" was added<br/>Primary outcome: For clarification, the sentence "Cause specific mortality will be described as per section 3.1 of the outcome form (haemorrhage, myocardial infarction, stroke, pulmonary embolism, pneumonia, malignancy, other)" was included under primary outcome.</p> <p><b>RATIONALE:</b><br/>Our original sample size estimate assumed a control group all-cause mortality risk of 10%. We estimated that a trial with 8,000 patients would have over 90% power (two sided alpha of 5%) to detect a 25% reduction (<math>RR=0.75</math>) in all-cause mortality. However, because the proportion of bleeding deaths is lower than expected, we might not find such a large (25%) reduction in all-cause mortality. The control group all-cause mortality risk will be about 10% by the time 12,000 patients are recruited. We expect about 60% of deaths will be due to bleeding. If tranexamic acid reduces bleeding deaths by 25% (<math>RR=0.75</math>), with no effect on non-bleeding deaths, the trial has over 80% power to detect a 15% (<math>RR=0.6 \times 0.75 + 0.4 \times 1.0 = 0.85</math>) reduction in all-cause mortality. In summary, increasing the sample size to 12,000 patients should provide adequate power to detect a plausible reduction in death from haemorrhage and all-cause mortality.</p> |
| 25 April 2019    | <p>Primary outcome: The primary outcome was changed from death from all causes within 28 days of randomisation to death from haemorrhage within 5 days of randomisation. All-cause and cause-specific mortality within 28 days will be reported as secondary outcomes.<br/>Secondary outcomes: "Death from haemorrhage within 28 days of randomisation" was added as secondary outcome.<br/>"Mortality: all-cause and cause-specific mortality within 28 days of randomisation" was added as secondary outcome.<br/>"Need for endoscopy" was added as secondary outcome.</p> <p><b>RATIONALE:</b><br/>Although the sample size remains at 12,000 as per the above justification, sample size calculations were rerun based on the amended primary outcome of death from haemorrhage within 5 days of randomisation. Blinded data from the HALT-IT trial show that only around 40% of deaths are due to bleeding and occur within 5 days of randomisation. Based on these estimates, a baseline event rate of 4% haemorrhage death within 5 days might reasonably be expected. Assuming a cumulative incidence of death due to bleeding of 4%, a study with 12,000 patients will have 85% power (two sided alpha = 5%) to detect a clinically important 25% relative reduction in death due to bleeding from 4% to 3%.</p>   |

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Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported