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) HALT-IT The Lancet figures (HALT-IT The Lancet figures.ppt) 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:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	1
Adolescents (12-17 years)	6
Adults (18-64 years)	7673
From 65 to 84 years	3491
85 years and over	838

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
Arm title	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.

Arm title	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.

Number of subjects in period 1	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 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 Units: Subjects			
Female	2142	2124	4266
Male	3852	3891	7743
Time from onset to randomisation, h Units: Subjects			
≤3	960	975	1935
>3–≤8	1607	1551	3158
>8	3427	3488	6915
Missing	0	1	1
Suspected location of bleeding Units: Subjects			
Lower	674	654	1328
Upper	5320	5361	10681
Hematemesis Units: Subjects			
Yes	4285	4240	8525
No	1709	1775	3484
Malaena or fresh blood per rectum Units: Subjects			
Yes	4573	4626	9199
No	1421	1389	2810
Suspected variceal bleeding Units: Subjects			
Yes	2694	2739	5433
No	3300	3276	6576
Suspected active bleeding Units: Subjects			
Yes	5247	5226	10473
No	747	789	1536
Systolic blood pressure, mm Hg Units: Subjects			

≥90	5222	5216	10438
76–89	577	577	1154
≤75	181	201	382
Missing	14	21	35
Herat rate, beats per min 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 Units: Subjects			
Yes	2574	2648	5222
No	3420	3367	6787
Rockall score Units: Subjects			
1-2	1419	1395	2814
3-4	2306	2332	4638
5-7	2269	2288	4557
Taking anticoagulants Units: Subjects			
Yes	528	500	1028
No	5422	5466	10888
Unknown	44	49	93
Emergency admission 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		

Attachments (see zip file)	HALT-IT Primary analysis/HALT-IT primary analysis.pptx

Statistical analyses

Statistical analysis title	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

Secondary: Complications-Any Thrombotic event	
End point title	Complications-Any Thrombotic event
End point description:	

End point type	Secondary
End point timeframe:	
Within 28 days of radomisation	

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

Statistical analysis title	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

Secondary: Complications-Venous events	
End point title	Complications-Venous 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: Venous events	48	26		

Statistical analyses

Statistical analysis title	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	

End point values	Tranexamic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5952	5977		
Units: Deep vein thrombosis	23	12		

Statistical analyses

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

End point values	Tranexamic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5952	5978		
Units: Respiratory failure	105	131		

Statistical analyses

Statistical analysis title	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	

End point values	Tranexamic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5952	5977		
Units: Cardiac event	100	89		

Statistical analyses

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

End point values	Tranexamic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5952	5977		
Units: Seizure	38	22		

Statistical analyses

Statistical analysis title	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			
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	
Cerebral infarction			
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	
Encephalopathy			
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	
Hepatic encephalopathy			
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	
Ischaemic stroke			
subjects affected / exposed	3 / 5985 (0.05%)	3 / 6004 (0.05%)	
occurrences causally related to treatment / all	3 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope			
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	
Transient ischaemic attack			
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	
Delirium			
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	
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 %

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

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

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

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

subjects affected / exposed	1 / 5985 (0.02%)	1 / 6004 (0.02%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	1 / 5985 (0.02%)	0 / 6004 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 5985 (0.02%)	1 / 6004 (0.02%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Crystal arthropathy			
subjects affected / exposed	0 / 5985 (0.00%)	1 / 6004 (0.02%)	
occurrences (all)	0	1	
Groin pain			
subjects affected / exposed	1 / 5985 (0.02%)	0 / 6004 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 5985 (0.00%)	1 / 6004 (0.02%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	1 / 5985 (0.02%)	1 / 6004 (0.02%)	
occurrences (all)	1	1	
Clostridium difficile infection			
subjects affected / exposed	1 / 5985 (0.02%)	3 / 6004 (0.05%)	
occurrences (all)	1	3	
Lower respiratory tract infection			
subjects affected / exposed	1 / 5985 (0.02%)	0 / 6004 (0.00%)	
occurrences (all)	1	0	
Oesophageal candidiasis			
subjects affected / exposed	0 / 5985 (0.00%)	3 / 6004 (0.05%)	
occurrences (all)	0	3	
Otitis externa			
subjects affected / exposed	0 / 5985 (0.00%)	1 / 6004 (0.02%)	
occurrences (all)	0	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 occurrences (all)	1 / 5985 (0.02%) 2	1 / 6004 (0.02%) 1	
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 5985 (0.00%) 0	1 / 6004 (0.02%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2017	Trial design: The sample size was increased from 8,000 to 12,000 patients Planned date of last patient enrolment: was changed from 30 November 2017 to 31 May 2019 Secondary outcomes: Death from haemorrhage was added as secondary outcome. 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 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. RATIONALE: 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 (RR=0.75) 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% (RR=0.75), with no effect on non-bleeding deaths, the trial has over 80% power to detect a 15% (RR=0.6×0.75 +0.4×1.0=0.85) 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.
25 April 2019	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. Secondary outcomes: “Death from haemorrhage within 28 days of randomisation” was added as secondary outcome. “Mortality: all-cause and cause-specific mortality within 28 days of randomisation” was added as secondary outcome. “Need for endoscopy” was added as secondary outcome. RATIONALE: 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%.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported