Clinical trial results:
A Phase III, case series clinical study of the reversal of the anticoagulant effects of dabigatran by intravenous administration of 5.0 g idarucizumab (BI 655075) in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures. RE-VERSE-AD (A study of the RE-VERSal Effects of Idarucizumab on Active Dabigatran) trial.

Summary

EudraCT number	2013-004813-41
Trial protocol	DE IE PT SE ES FI EE LV CZ IT SK NL BE AT NO DK FR
Global end of trial date	20 October 2016

Results information

Result version number	v1 (current)
This version publication date	20 September 2017
First version publication date	20 September 2017

Trial information

Trial identification

Sponsor protocol code	1321.3

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	173 Binger Strasse, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com

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	18 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 July 2016
Global end of trial reached?	Yes
Global end of trial date	20 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate reversal of the anticoagulant effect of dabigatran. The secondary objectives were the assessment of bleeding, clinical outcomes, safety and the pharmacokinetics of dabigatran in the presence of idarucizumab.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 May 2014
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	Argentina: 1
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 48
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Colombia: 4
Country: Number of subjects enrolled	Czech Republic: 13
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Finland: 13
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	India: 2
Country: Number of subjects enrolled	Ireland: 7
Country: Number of subjects enrolled	Israel: 15
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Japan: 12
Country: Number of subjects enrolled	Mexico: 1

Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	New Zealand: 150
Country: Number of subjects enrolled	Norway: 13
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	South Africa: 4
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Spain: 38
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 50
Worldwide total number of subjects	515
EEA total number of subjects	224

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	50
From 65 to 84 years	349
85 years and over	116

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all inclusion/exclusion criteria. Subjects were not to be enrolled if any one of the specific entry criteria were violated.

Period 1

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

Blinding implementation details:

This is an Open label, Non randomised and Uncontrolled study.

Arms

Are arms mutually exclusive?	Yes
Arm title	idarucizumab (Group A)

Arm description:

Patients who were treated with dabigatran and who had uncontrolled or life threatening bleeding that required urgent medical or surgical intervention were administered idarucizumab 5 g (two 2.5 g vials) as an intravenous (IV) infusion. A single vial contains 2.5 g of idarucizumab. Patients received a 2.5 g vial of study medication and a second 2.5-g vial within the next 15 minutes.

Arm type	Experimental
Investigational medicinal product name	idarucizumab 5 g
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients who were treated with dabigatran and who had uncontrolled or life threatening bleeding that required urgent
medical or surgical intervention were administered idarucizumab 5 g (two 2.5 g vials) as an intravenous (IV) infusion. A single vial contains 2.5 g of idarucizumab. Patients received a 2.5 g vial of study medication and a second 2.5-g vial within the next 15 minutes.

Arm title	idarucizumab (Group B)

Arm description:

Patients who were treated with dabigatran and who may not have been bleeding, but required an emergency surgery or other invasive procedure for a condition other than bleeding where therapeutic anticoagulation might have increased the risk of intra- and post-operative bleeding were administered idarucizumab 5 g (two 2.5 g vials) as an intravenous (IV) infusion. A single vial contains 2.5 g of idarucizumab. Patients received a 2.5 g vial of study medication and a second 2.5-g vial within the next 15 minutes.

Arm type	Experimental
Investigational medicinal product name	idarucizumab 5 g
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients who were treated with dabigatran and who may not have been bleeding, but required an emergency surgery or

other invasive procedure for a condition other than bleeding where therapeutic anticoagulation might have increased the
risk of intra- and post-operative bleeding were administered idarucizumab 5 g (two 2.5 g vials) as an intravenous (IV)
infusion. A single vial contains 2.5 g of idarucizumab. Patients received a 2.5 g vial of study medication and a second
2.5-g vial within the next 15 minutes.

Number of subjects in period 1[1]	idarucizumab (Group A)	idarucizumab (Group B)
Started	301	202
Completed	222	146
Not completed	79	56
Protocol deviation	6	8
Adverse event, non-fatal	57	38
Consent withdrawn by subject	10	3
Other than stated above	2	3
Lost to follow-up	4	4

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on the patients who successfully completed the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	idarucizumab (Group A)
Reporting group description:	
Patients who were treated with dabigatran and who had uncontrolled or life threatening bleeding that required urgent medical or surgical intervention were administered idarucizumab 5 g (two 2.5 g vials) as an intravenous (IV) infusion. A single vial contains 2.5 g of idarucizumab. Patients received a 2.5 g vial of study medication and a second 2.5-g vial within the next 15 minutes.	
Reporting group title	idarucizumab (Group B)
Reporting group description:	
Patients who were treated with dabigatran and who may not have been bleeding, but required an emergency surgery or other invasive procedure for a condition other than bleeding where therapeutic anticoagulation might have increased the risk of intra- and post-operative bleeding were administered idarucizumab 5 g (two 2.5 g vials) as an intravenous (IV) infusion. A single vial contains 2.5 g of idarucizumab. Patients received a 2.5 g vial of study medication and a second 2.5-g vial within the next 15 minutes.	

Reporting group values	idarucizumab (Group A)	idarucizumab (Group B)	Total
Number of subjects	301	202	503
Age categorical			
Treated set: Treated Set is defined as all patients who were administered idarucizumab.			
Units: Subjects			

Age Continuous			
Treated set: Treated Set is defined as all patients who were administered idarucizumab.			
Units: years			
arithmetic mean	77.1	75.9	
standard deviation	± 10.4	± 10.5	-
Gender, Male/Female			
Units: Subjects			
Female	129	100	229
Male	172	102	274

End points

End points reporting groups

Reporting group title	idarucizumab (Group A)

Reporting group description:

Patients who were treated with dabigatran and who had uncontrolled or life threatening bleeding that required urgent medical or surgical intervention were administered idarucizumab 5 g (two 2.5 g vials) as an intravenous (IV) infusion. A single vial contains 2.5 g of idarucizumab. Patients received a 2.5 g vial of study medication and a second 2.5-g vial within the next 15 minutes.

Reporting group title	idarucizumab (Group B)

Reporting group description:

Patients who were treated with dabigatran and who may not have been bleeding, but required an emergency surgery or other invasive procedure for a condition other than bleeding where therapeutic anticoagulation might have increased the risk of intra- and post-operative bleeding were administered idarucizumab 5 g (two 2.5 g vials) as an intravenous (IV) infusion. A single vial contains 2.5 g of idarucizumab. Patients received a 2.5 g vial of study medication and a second 2.5-g vial within the next 15 minutes.

Subject analysis set title	ICH (Group A)
Subject analysis set type	Full analysis

Subject analysis set description:

Group A patients with baseline intracranial hemorrhage (ICH).

Full analysis is actually treated set.

Subject analysis set title	Non-ICH (Group A)
Subject analysis set type	Full analysis

Subject analysis set description:

Group A patients with baseline non-intracranial hemorrhage (non-ICH).

Full analysis is actually treated set.

Subject analysis set title	idarucizumab (Group A & B)
Subject analysis set type	Full analysis

Subject analysis set description:

In Group A the patients who were treated with dabigatran and who had uncontrolled or life threatening bleeding that required urgent medical or surgical intervention were administered idarucizumab 5 g (two 2.5 g vials) as an intravenous (IV) infusion. A single vial contains 2.5 g of idarucizumab. Patients received a 2.5 g vial of study medication and a second 2.5-g vial within the next 15 minutes. In Group B the patients who were treated with dabigatran and who may not have been bleeding, but required an emergency surgery or other invasive procedure for a condition other than bleeding where therapeutic anticoagulation might have increased the risk of intra- and post-operative bleeding were administered idarucizumab 5 g (two 2.5 g vials) as an intravenous (IV) infusion. A single vial contains 2.5 g of idarucizumab. Patients received a 2.5 g vial of study medication and a second 2.5-g vial within the next 15 minutes.
Full analysis is actually treated set.

Primary: Maximum reversal of anticoagulant effect of dabigatran based on central laboratory determination of dTT or ECT

End point title	Maximum reversal of anticoagulant effect of dabigatran based on central laboratory determination of dTT or ECT[1]

End point description:

Maximum reversal of anticoagulant effect of dabigatran based on central laboratory determination of diluted thrombin time (dTT) or ecarin clotting time (ECT), at any time point from the end of the first infusion up to 4 hours after the last infusion. Reversal is defined for patients with at least one post−dose coagulation test results and pre−dose result higher than 100% ULN (evaluable patients). Reversal is calculated as 100* (pre−dose value minus post dose value)/(pre−dose value minus 100% x ULN); if calculated reversal is > 100, it was set to 100.

End point type	Primary

End point timeframe:

from the end of the first infusion up to 4 hours after the last infusion on Day 1

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis test were tested.

End point values	idarucizumab (Group A)	idarucizumab (Group B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301[2]	202[3]		
Units: percentage				
median (confidence interval 95%)				
dTT (N=244; 152)	100 (100 to 100)	100 (100 to 100)		
ECT (N= 276; 185)	100 (100 to 100)	100 (100 to 100)		

Notes:

[2] - Treated Set

[3] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Reversal of aPTT and TT from central laboratory

End point title	Reversal of aPTT and TT from central laboratory

End point description:

Reversal of anticoagulation as measured by Activated Partial Thromboplastin Time (aPTT) and Thrombin time (TT) from central laboratory, at any time point since the end of first infusion up to 4 hours after the completion of the last infusion. Reversal is defined for patients with at least one post−dose coagulation test results and pre−dose result higher than 100% ULN (evaluable patients). Reversal is calculated as 100* (pre−dose value minus post dose value)/(pre−dose value minus 100% x ULN); if calculated reversal is > 100, it was set to 100.

End point type	Secondary

End point timeframe:

from the end of the first infusion up to 4 hours after the last infusion on Day 1

End point values	idarucizumab (Group A)	idarucizumab (Group B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301[4]	202[5]		
Units: percentage				
median (confidence interval 95%)				
aPTT (N=232; 141)	100 (100 to 100)	100 (100 to 100)		
TT (N=278; 188)	100 (100 to 100)	100 (100 to 100)		

Notes:

[4] - Treated Set

[5] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of reversal

End point title	Duration of reversal

End point description:

Duration of reversal, defined as the time period a patient remained completely reversed based on dTT or ECT, up to 24 hours or re-starting the treatment of dabigatran.

End point type	Secondary

End point timeframe:

from the first infusion up to 24 hours after the last infusion on Day 1

End point values	idarucizumab (Group A)	idarucizumab (Group B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301[6]	202[7]		
Units: hours				
arithmetic mean (standard deviation)				
ECT (N= 276; 185)	13.2 (± 10)	12.8 (± 9.7)		
dTT (N=244; 152)	19.8 (± 6.7)	18.8 (± 7.6)		

Notes:

[6] - Treated Set

[7] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of major/life-threatening/fatal bleeding (for group B only) intraoperatively

End point title	Occurrence of major/life-threatening/fatal bleeding (for group B only) intraoperatively[8]

End point description:

Occurrence of major/life-threatening/fatal bleeding (for group B only) intraoperatively and up to 24 hours post-surgery were classified according to major or life-threatening bleeding (ISTH [International Society for Thrombosis and Hemostasis] definition). 95% CI is from Clopper-Pearson method.

End point type	Secondary

End point timeframe:

within 24 hours of surgery

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	idarucizumab (Group B)			
Subject group type	Reporting group			
Number of subjects analysed	202[9]			
Units: percentage of participants				
number (confidence interval 95%)	3 (1.1 to 6.5)			

Notes:

[9] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to cessation of bleeding (for Group A only)

End point title	Time to cessation of bleeding (for Group A only)

End point description:

Time to cessation of bleeding (for Group A only) since first infusion up to 24 hours after the completion of second infusion; bleeding status was to be categorized before and at several time points after treatment.

End point type	Secondary

End point timeframe:

from the first infusion up to 24 hours after the last infusion on Day 1

End point values	ICH (Group A)	Non-ICH (Group A)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41[10]	134[11]		
Units: hours				
median (confidence interval 95%)	10.73 (4.8 to 15.73)	2.49 (2.18 to 3.93)		

Notes:

[10] - Treated Set with patients who stopped bleeding within 24 hours

[11] - Treated Set with patients who stopped bleeding within 24 hours

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin,1 of unbound sum (free) dabigatran

End point title	Cmin,1 of unbound sum (free) dabigatran

End point description:

Cmin,1 (Minimum concentrations at any time point since the end of first vial of idarucizumab up to 4 hours after the completion of second vial) of unbound sum (free) dabigatran, provided that two vials given not more than 15 min apart in group A and B.
The Pharmacokinetic Set (PK Set): This analysis set was used for all PK analyses and was defined as all patients in the Treated Set who provided at least one PK data point.

End point type	Secondary

End point timeframe:

Since the end of first vial of idarucizumab up to 4 hours after the completion of second vial

End point values	idarucizumab (Group A & B)			
Subject group type	Subject analysis set			
Number of subjects analysed	493[12]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	1.12 (± 61.2)			

Notes:

[12] - PK Set

Statistical analyses

No statistical analyses for this end point

Secondary: Reversal of anticoagulation as measured by diluted Thrombin Time (dTT) or Ecarin Clotting Time (ECT) after the first vial of idarucizumab and before the start of second vial

End point title	Reversal of anticoagulation as measured by diluted Thrombin Time (dTT) or Ecarin Clotting Time (ECT) after the first vial of idarucizumab and before the start of second vial

End point description:

Reversal of anticoagulation as measured by diluted Thrombin Time (dTT) or Ecarin Clotting Time (ECT) after the first vial of
idarucizumab and before the start of second vial. Reversal is defined for patients with at least one post−dose coagulation test results and pre−dose result higher than 100% ULN (evaluable patients). Reversal is calculated as 100*(pre−dose value minus post dose value)/(pre−dose value minus 100% x ULN); if calculated reversal is > 100, it was set to 100.

End point type	Secondary

End point timeframe:

after the first vial of idarucizumab and before the start of second vial on Day1

End point values	idarucizumab (Group A)	idarucizumab (Group B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301[13]	202[14]		
Units: percentage				
median (confidence interval 95%)				
dTT (N= 240; N=150)	100 (100 to 100)	100 (100 to 100)		
ECT (N= 271; N=182)	100 (100 to 100)	100 (100 to 100)		

Notes:

[13] - Treated Set

[14] - Treated Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first vial of idarucizumab until end of study (90 ± 7 days after the second vial).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	idarucizumab (Group B)

Reporting group description:

Patients who were treated with dabigatran and who may not have been bleeding, but required an emergency surgery or other invasive procedure for a condition other than bleeding where therapeutic anticoagulation might have increased the risk of intra- and post-operative bleeding were administered idarucizumab 5 g (two 2.5 g vials) as an intravenous (IV) infusion. A single vial contains 2.5 g of idarucizumab. Patients received a 2.5 g vial of study medication and a second 2.5-g vial within the next 15 minutes.

Reporting group title	idarucizumab (Group A)

Reporting group description:

Patients who were treated with dabigatran and who had uncontrolled or life threatening bleeding that required urgent medical or surgical intervention were administered idarucizumab 5 g (two 2.5 g vials) as an intravenous (IV) infusion. A single vial contains 2.5 g of idarucizumab. Patients received a 2.5 g vial of study medication and a second 2.5-g vial within the next 15 minutes.

Serious adverse events	idarucizumab (Group B)	idarucizumab (Group A)	
Total subjects affected by serious adverse events			
subjects affected / exposed	106 / 202 (52.48%)	160 / 301 (53.16%)	
number of deaths (all causes)	40	61	
number of deaths resulting from adverse events	2	3	
Vascular disorders			
Aortic aneurysm rupture			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Circulatory collapse			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	3 / 202 (1.49%)	7 / 301 (2.33%)	
occurrences causally related to treatment / all	0 / 3	1 / 7	

deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	2 / 202 (0.99%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	2 / 202 (0.99%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 202 (0.50%)	3 / 301 (1.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct cancer			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colon cancer			
subjects affected / exposed	0 / 202 (0.00%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon neoplasm			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Genital neoplasm malignant female			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal adenocarcinoma			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	1 / 202 (0.50%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal adenocarcinoma			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adhesion			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 202 (0.99%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Multiple organ dysfunction syndrome			

subjects affected / exposed	4 / 202 (1.98%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 1	
Oedema peripheral			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden cardiac death			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden death			
subjects affected / exposed	0 / 202 (0.00%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Psychiatric disorders			
Delirium			
subjects affected / exposed	8 / 202 (3.96%)	13 / 301 (4.32%)	
occurrences causally related to treatment / all	0 / 9	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucinations, mixed			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 202 (0.50%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Brain contusion			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis radiation			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft thrombosis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Head injury			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site irritation			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 202 (0.00%)	9 / 301 (2.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 2	
Subdural haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemothorax			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 202 (0.00%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 202 (0.00%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 202 (0.99%)	1 / 301 (0.33%)	
occurrences causally related to	1 / 2	0 / 1	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 202 (0.50%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac amyloidosis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	9 / 202 (4.46%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	1 / 9	0 / 2	

deaths causally related to treatment / all	1 / 4	0 / 1	
Cardiac failure			
subjects affected / exposed	4 / 202 (1.98%)	11 / 301 (3.65%)	
occurrences causally related to treatment / all	0 / 4	0 / 12	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cardiac failure acute			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 202 (0.00%)	3 / 301 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 202 (0.99%)	10 / 301 (3.32%)	
occurrences causally related to treatment / all	1 / 2	0 / 11	
deaths causally related to treatment / all	1 / 1	0 / 5	
Cardiac tamponade			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiogenic shock			
subjects affected / exposed	2 / 202 (0.99%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Coronary artery disease			
subjects affected / exposed	2 / 202 (0.99%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mitral valve incompetence			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 202 (0.50%)	3 / 301 (1.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Myocardial ischaemia			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pericardial effusion			
subjects affected / exposed	2 / 202 (0.99%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular tachycardia			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Acute pulmonary oedema			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Apnoea			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphonia			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 202 (1.49%)	4 / 301 (1.33%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	0 / 202 (0.00%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonitis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	2 / 202 (0.99%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 202 (1.98%)	5 / 301 (1.66%)	
occurrences causally related to treatment / all	0 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary hypertension			
subjects affected / exposed	0 / 202 (0.00%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	3 / 202 (1.49%)	7 / 301 (2.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory arrest			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	4 / 202 (1.98%)	7 / 301 (2.33%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhagic anaemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypocoagulable state			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (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			
Basal ganglia haemorrhage			

subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain injury			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain oedema			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain stem haemorrhage			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Brain stem syndrome			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebellar syndrome			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 202 (0.00%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral infarction			
subjects affected / exposed	1 / 202 (0.50%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	

occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Chorea			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Embolic cerebral infarction			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 202 (0.50%)	5 / 301 (1.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 4	
Headache			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial mass			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic stroke			
subjects affected / exposed	2 / 202 (0.99%)	5 / 301 (1.66%)	
occurrences causally related to treatment / all	1 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Monoplegia			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Seizure			
subjects affected / exposed	1 / 202 (0.50%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Simple partial seizures			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
Amaurosis fugax			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous floaters			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal wall haematoma			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	0 / 202 (0.00%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive duodenitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	2 / 202 (0.99%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 202 (0.99%)	4 / 301 (1.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	

Gastrointestinal mucosal necrosis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	2 / 202 (0.99%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal ulcer			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	2 / 202 (0.99%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	2 / 202 (0.99%)	0 / 301 (0.00%)	

occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 202 (0.50%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis necrotising			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 202 (2.97%)	5 / 301 (1.66%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Anuria			
subjects affected / exposed	0 / 202 (0.00%)	3 / 301 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	3 / 202 (1.49%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	5 / 202 (2.48%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic hepatitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin necrosis			
subjects affected / exposed	2 / 202 (0.99%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous emphysema			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device loosening			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroid haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gout			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 202 (0.50%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Starvation			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infection			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infectious pleural effusion			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinitis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site joint infection			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	2 / 202 (0.99%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 202 (3.47%)	14 / 301 (4.65%)	
occurrences causally related to treatment / all	0 / 8	0 / 15	
deaths causally related to treatment / all	0 / 2	0 / 4	
Pneumonia bacterial			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Postoperative wound infection			
subjects affected / exposed	2 / 202 (0.99%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	5 / 202 (2.48%)	7 / 301 (2.33%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 3	0 / 2	
Septic shock			
subjects affected / exposed	11 / 202 (5.45%)	2 / 301 (0.66%)	
occurrences causally related to treatment / all	0 / 11	0 / 2	
deaths causally related to treatment / all	0 / 8	0 / 2	
Urinary tract infection			
subjects affected / exposed	0 / 202 (0.00%)	6 / 301 (1.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 202 (0.50%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	idarucizumab (Group B)	idarucizumab (Group A)	
Total subjects affected by non-serious adverse events subjects affected / exposed	86 / 202 (42.57%)	139 / 301 (46.18%)	
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	15 / 202 (7.43%) 16	17 / 301 (5.65%) 17	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	11 / 202 (5.45%) 11	13 / 301 (4.32%) 18	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	11 / 202 (5.45%) 11 6 / 202 (2.97%) 6	9 / 301 (2.99%) 9 27 / 301 (8.97%) 29	
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	14 / 202 (6.93%) 15 6 / 202 (2.97%) 7	17 / 301 (5.65%) 19 23 / 301 (7.64%) 26	
Psychiatric disorders Confusional state subjects affected / exposed occurrences (all)	13 / 202 (6.44%) 13	8 / 301 (2.66%) 8	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea	20 / 202 (9.90%) 21 18 / 202 (8.91%) 18	33 / 301 (10.96%) 34 14 / 301 (4.65%) 16	

subjects affected / exposed occurrences (all)	18 / 202 (8.91%) 20	21 / 301 (6.98%) 24	
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	 6 / 202 (2.97%) 6	 18 / 301 (5.98%) 18	
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	 8 / 202 (3.96%) 9	 23 / 301 (7.64%) 27	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	 17 / 202 (8.42%) 18	 35 / 301 (11.63%) 41	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 June 2015	Clarified the biomarkers to be used for the primary analysis, included additional measures of efficacy and safety, and clarified/updated eligibility criteria, procedures, and planned analyses.
28 October 2015	increased the estimated number of patients entered/treated in the study to approximately 500 patients or until each participating country had enrolled sufficient patients to satisfy their regulatory requirements, or until idarucizumab was commercially available in that country. In addition, this amendment allowed for an additional idarucizumab dose of 5 g in rare instances.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported