Clinical trial results:
Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who Have Acute Major Bleeding (ANNEXA-4).

Summary

EudraCT number	2015-001785-26
Trial protocol	NL GB BE DE FR
Global end of trial date	24 September 2020

Results information

Result version number	v1 (current)
This version publication date	13 November 2021
First version publication date	13 November 2021

Trial information

Trial identification

Sponsor protocol code	14-505

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02329327
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals, Inc.
Sponsor organisation address	121 Seaport Boulevard, Boston, MA, United States, 02210
Public contact	European Clinical Trial Information, Alexion Pharmaceuticals, Inc., +33 147100606, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Pharmaceuticals, Inc., +33 147100606, clinicaltrials.eu@alexion.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	24 September 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the hemostatic efficacy of andexanet alfa (andexanet) in participants receiving a factor Xa (FXa) inhibitor (apixaban, rivaroxaban, edoxaban, enoxaparin) who were experiencing an acute major bleed. The safety of andexanet was also studied.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 April 2015
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	Belgium: 19
Country: Number of subjects enrolled	United States: 205
Country: Number of subjects enrolled	Japan: 19
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Germany: 179
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Netherlands: 12
Worldwide total number of subjects	479
EEA total number of subjects	223

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)	47
From 65 to 84 years	306
85 years and over	126

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Attempts were made to enroll participants on direct FXa inhibitors as well as those on indirect FXa inhibitors, and to limit the percentage of enrolled participants receiving indirect FXa inhibitors.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Andexanet

Arm description:

Participants received andexanet as an intravenous (IV) bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.

Arm type	Experimental
Investigational medicinal product name	Andexanet
Investigational medicinal product code	
Other name	ALXN2070, Andexanet Alfa, PRT064445, Ondexxya
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

There were 2 possible dosing regimens: Low dose = 400 milligram (mg) bolus plus 4 mg/minute continuous infusion for 120 minutes; High dose = 800 mg bolus plus 8 mg/minute continuous infusion for 120 minutes.

Arm title	Andexanet - Additional Participants

Arm description:

Two additional participants received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. Data from these 2 participants were obtained and evaluated after the data cutoff date of 30-June-2020 and, as such, are presented separately.

Arm type	Experimental
Investigational medicinal product name	Andexanet
Investigational medicinal product code	
Other name	ALXN2070, Andexanet Alfa, PRT064445, Ondexxya
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

There were 2 possible dosing regimens: Low dose = 400 mg bolus plus 4 mg/minute continuous infusion for 120 minutes; High dose = 800 mg bolus plus 8 mg/minute continuous infusion for 120 minutes.

Number of subjects in period 1	Andexanet	Andexanet - Additional Participants
Started	477	2
Received At Least 1 Dose of Study Drug	477	2
Efficacy Population	347 [1]	2
Death	3 [2]	0 [3]
Completed	392	2
Not completed	85	0
Adverse event, serious fatal	78	-
Consent withdrawn by subject	3	-
Lost to follow-up	4	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: All participants who received at least 1 dose of study drug and who met protocol-specified criteria for bleeding and anti-fXa levels.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These deaths occurred during the follow-up period.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These deaths occurred during the follow-up period.

Baseline characteristics

Reporting groups	
Reporting group title	Andexanet
Reporting group description:	
Participants received andexanet as an intravenous (IV) bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.	
Reporting group title	Andexanet - Additional Participants
Reporting group description:	
Two additional participants received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. Data from these 2 participants were obtained and evaluated after the data cutoff date of 30-June-2020 and, as such, are presented separately.	

Reporting group values	Andexanet	Andexanet - Additional Participants	Total
Number of subjects	477	2	479
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	46	1	47
From 65-84 years	305	1	306
85 years and over	126	0	126
Age Continuous Units: years			
arithmetic mean	77.9	71.0	
standard deviation	± 10.66	± 11.31	-
Sex: Female, Male Units: participants			
Female	218	1	219
Male	259	1	260
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	16	0	16
Not Hispanic or Latino	449	2	451
Unknown or Not Reported	12	0	12
Race/Ethnicity, Customized			
Asian participants and American Indian or Alaska Native participants are reported as Other.			
Units: Subjects			
White	414	0	414
Black or African American	29	0	29
Other	25	2	27
Missing	9	0	9

Region of Enrollment Units: Subjects			
North America	212	0	212
Europe	248	0	248
Japan	17	2	19
FXa Inhibitor Units: Subjects			
Apixaban	245	0	245
Rivaroxaban	174	2	176
Edoxaban	36	0	36
Enoxaparin	22	0	22
Bleed Type			
Endpoint Adjudication Committee (EAC) determined if each participant met the bleeding entry criteria for inclusion in the Efficacy Population.			
Units: Subjects			
Gastrointestinal	109	0	109
Intracranial Hemorrhage	329	2	331
Other	39	0	39

End points

End points reporting groups

Reporting group title	Andexanet

Reporting group description:

Participants received andexanet as an intravenous (IV) bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.

Reporting group title	Andexanet - Additional Participants

Reporting group description:

Two additional participants received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. Data from these 2 participants were obtained and evaluated after the data cutoff date of 30-June-2020 and, as such, are presented separately.

Subject analysis set title	FXa Inhibitor: Apixaban
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who had recently received FXa inhibitor apixaban received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.

Subject analysis set title	FXa Inhibitor: Rivaroxaban
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who had recently received FXa inhibitor rivaroxaban received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.

Subject analysis set title	FXa Inhibitor: Edoxaban
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who had recently received FXa inhibitor edoxaban received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.

Subject analysis set title	FXa Inhibitor: Enoxaparin
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who had recently received FXa inhibitor enoxaparin received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.

Subject analysis set title	Bleed Type: Gastrointestinal
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with gastrointestinal bleeding who had recently received an FXa inhibitor received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.

Subject analysis set title	Bleed Type: Intracranial Hemorrhage
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with an intracranial hemorrhage who had recently received an FXa inhibitor received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.

Subject analysis set title	Bleed Type: Other
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with other types of bleeding who had recently received an FXa inhibitor received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.

Subject analysis set title	Andexanet: Low Dose

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who had recently received FXa inhibitors received andexanet as an IV 400-mg bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion of 480 mg (4 mg/minute) administered over ~120 minutes.

Subject analysis set title	Andexanet: High Dose
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who had recently received FXa inhibitors received andexanet as an IV 800-mg bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion of 960 mg (8 mg/minute) administered over ~120 minutes.

Subject analysis set title	Overall
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who had recently received FXa inhibitor received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. Does not include the 2 additional participants whose data were obtained and evaluated after the data cutoff date of 30-June-2020.

Subject analysis set title	FXa Inhibitor: Rivaroxaban - Additional Participants
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Two additional participants who had recently received FXa inhibitor rivaroxaban received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. Data from these 2 participants were obtained and evaluated after the data cutoff date of 30-June-2020 and, as such, are presented separately.

Subject analysis set title	Bleed Type: Intracranial Hemorrhage - Additional Participants
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Two additional participants with an intracranial hemorrhage who had recently received an FXa inhibitor received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. Data from these 2 participants were obtained and evaluated after the data cutoff date of 30-June-2020 and, as such, are presented separately.

Subject analysis set title	Andexanet: Low Dose - Additional Participant
Subject analysis set type	Sub-group analysis

Subject analysis set description:

One additional participant who had recently received FXa inhibitors received andexanet as an IV 400-mg bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion of 480 mg (4 mg/minute) administered over ~120 minutes. Data from this participant were obtained and evaluated after the data cutoff date of 30-June-2020 and, as such, are presented separately.

Subject analysis set title	Andexanet: High Dose - Additional Participant
Subject analysis set type	Sub-group analysis

Subject analysis set description:

One additional participant who had recently received FXa inhibitors received andexanet as an IV 800-mg bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion of 960 mg (8 mg/minute) administered over ~120 minutes. Data from this participant were obtained and evaluated after the data cutoff date of 30-June-2020 and, as such, are presented separately.

Primary: Percent Change From Baseline In Anti-fXa Activity By FXa Inhibitor

End point title	Percent Change From Baseline In Anti-fXa Activity By FXa Inhibitor[1]

End point description:

Anti-fXa activity was measured to assess the ability of andexanet to reverse the anticoagulant effect of FXa inhibitors. Baseline was defined as the last value obtained prior to the start of the andexanet bolus. The change from baseline was calculated as the reduction in anti-fXa activity from baseline to the on-treatment nadir (that is, the minimum value between end of bolus and end of infusion). Percent reduction was calculated as the ratio between the maximum change from baseline and the baseline value, multiplied by 100.

End point type	Primary

End point timeframe:

Baseline, 12 Hours (post infusion)

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: Quantitative statistical analysis (for example, a p-value) was not performed for this end point. Descriptive statistics are included (median and CI).

End point values	FXa Inhibitor: Apixaban	FXa Inhibitor: Rivaroxaban	FXa Inhibitor: Edoxaban	FXa Inhibitor: Enoxaparin
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	172	130	28	17
Units: Percent Change				
median (confidence interval 95%)	-93.3 (-94.2 to -92.5)	-94.1 (-95.1 to -93.0)	-71.3 (-82.3 to -65.2)	-75.41 (-79.17 to -66.67)

End point values	FXa Inhibitor: Rivaroxaban - Additional Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: Percent Change				
median (confidence interval 95%)	-96.3 (-98.3 to -94.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Participants Achieving Hemostatic Efficacy

End point title	Participants Achieving Hemostatic Efficacy[2]

End point description:

Hemostatic efficacy was achieved when the body had time to produce thrombin and a subsequent clot and was rated by the EAC as: excellent; good; poor/none; not evaluable due to non-administrative reasons; not evaluable due to administrative reasons. These ratings were based on pre-specified criteria that were included in the EAC Charter. The EAC was blinded to anti-fXa activity levels. Participant results were classified as either success or failure based on the hemostatic efficacy rating (success = excellent/good, failure = poor/none). Participants rated by the EAC as non-evaluable due to administrative reasons were excluded from the analysis of hemostatic efficacy.

End point type	Primary

End point timeframe:

12 Hours (post infusion)

Notes:

[2] - 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: Quantitative statistical analysis (for example, a p-value) was not performed for this end point. Descriptive statistics are included (median and CI).

End point values	FXa Inhibitor: Apixaban	FXa Inhibitor: Rivaroxaban	FXa Inhibitor: Edoxaban	FXa Inhibitor: Enoxaparin
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	169	127	28	16
Units: Percent Change				
Excellent/Good	134	102	22	14
Poor/None	35	25	6	2

End point values	Bleed Type: Gastrointestinal	Bleed Type: Intracranial Hemorrhage	Bleed Type: Other	Andexanet: Low Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	74	244	22	269
Units: Percent Change				
Excellent/Good	61	193	18	218
Poor/None	13	51	4	51

End point values	Andexanet: High Dose	Overall	FXa Inhibitor: Rivaroxaban - Additional Participants	Bleed Type: Intracranial Hemorrhage - Additional Participants
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	71	240	2	2
Units: Percent Change				
Excellent/Good	54	272	2	2
Poor/None	17	68	0	0

End point values	Andexanet: Low Dose - Additional Participant	Andexanet: High Dose - Additional Participant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1	1		
Units: Percent Change				
Excellent/Good	1	1		
Poor/None	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline In Anti-fXa Activity By Hemostatic Efficacy

End point title	Percent Change From Baseline In Anti-fXa Activity By Hemostatic Efficacy

End point description:

This outcome measure assessed the relationship between hemostatic efficacy and anti-fXa activity in participants receiving an FXa inhibitor who had acute major bleeding. Anti-fXa activity was measured to assess the ability of andexanet to reverse the anticoagulant effect of FXa inhibitors. Baseline was defined as the last value obtained prior to the start of the andexanet bolus. Hemostatic efficacy was achieved when the body had time to produce thrombin and a subsequent clot and was rated by the EAC as: excellent; good; poor/none; not evaluable due to non-administrative reasons; not evaluable due to administrative reasons.

End point type	Secondary

End point timeframe:

Baseline, 12 Hours (post infusion)

End point values	FXa Inhibitor: Apixaban	FXa Inhibitor: Rivaroxaban	FXa Inhibitor: Edoxaban	FXa Inhibitor: Enoxaparin
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	134	102	22	14
Units: Percent Change				
median (confidence interval 95%)				
Excellent/Good	-93.4 (-94.3 to -92.6)	-94.6 (-95.2 to -93.5)	-75.8 (-84.4 to -65.2)	-75.20 (-77.08 to -65.91)
Poor/None	-93.3 (-95.3 to -90.6)	-92.4 (-96.5 to -85.0)	-65.2 (-85.3 to 3.0)	-78.44 (-82.46 to -74.42)

End point values	FXa Inhibitor: Rivaroxaban - Additional Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	2[3]			
Units: Percent Change				
median (confidence interval 95%)				
Excellent/Good	-96.3 (-98.3 to -94.3)			
Poor/None	999 (999 to 999)			

Notes:

[3] - 999 = Not available due to 0 participants having a hemostatic efficacy of Poor/None.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 through Day 37.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Andexanet - Additional Participants

Reporting group description:

Two additional participants received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. Data from these 2 participants were obtained and evaluated after the data cutoff date of 30-June-2020 and, as such, are presented separately.

Reporting group title	Andexanet

Reporting group description:

Participants received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.

Serious adverse events	Andexanet - Additional Participants	Andexanet	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	200 / 477 (41.93%)	
number of deaths (all causes)	0	81	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anaplastic Astrocytoma			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Cancer			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain Neoplasm			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal Stromal Tumour			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Cancer Metastatic			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer Metastatic			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
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	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 2 (0.00%)	4 / 477 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep Vein Thrombosis			
subjects affected / exposed	0 / 2 (0.00%)	5 / 477 (1.05%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aorto-Duodenal Fistula			

subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac Artery Occlusion			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock Haemorrhagic			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Tracheostomy			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Drainage			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
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			
Multi-Organ Failure			
subjects affected / exposed	0 / 2 (0.00%)	5 / 477 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Death			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General Physical Health Deterioration			
subjects affected / exposed	0 / 2 (0.00%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Cardiac Death			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gait Disturbance			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Death			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Swelling			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Social Stay Hospitalisation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
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			
Pneumonia Aspiration			
subjects affected / exposed	0 / 2 (0.00%)	8 / 477 (1.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory Failure			
subjects affected / exposed	0 / 2 (0.00%)	12 / 477 (2.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Respiratory Failure			
subjects affected / exposed	0 / 2 (0.00%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	0 / 2 (0.00%)	8 / 477 (1.68%)	
occurrences causally related to treatment / all	0 / 0	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Oedema			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Distress			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Pulmonary Oedema			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial Secretion Retention			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
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	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Acidosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Arrest			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental Status Changes			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental Disorder Due To A General Medical Condition			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
CSF Red Blood Cell Count Positive			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT Prolonged			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Electroencephalogram Abnormal			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases Increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Function Test Abnormal			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin I Increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Subdural Haematoma			
subjects affected / exposed	0 / 2 (0.00%)	8 / 477 (1.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain Herniation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion Related Reaction			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical Vertebral Fracture			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lumbar Vertebral Fracture			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 2 (0.00%)	5 / 477 (1.05%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	0 / 2 (0.00%)	6 / 477 (1.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic Shock			
subjects affected / exposed	0 / 2 (0.00%)	4 / 477 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	0 / 2 (0.00%)	5 / 477 (1.05%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	0 / 2 (0.00%)	3 / 477 (0.63%)	
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	0 / 2 (0.00%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	0 / 2 (0.00%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right Ventricular Failure			

subjects affected / exposed	0 / 2 (0.00%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Ischaemia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Thrombosis			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block Complete			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Ventricular Thrombosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-Respiratory Arrest			

subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Node Dysfunction			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic Stroke			
subjects affected / exposed	0 / 2 (0.00%)	10 / 477 (2.10%)	
occurrences causally related to treatment / all	0 / 0	6 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	0 / 2 (0.00%)	8 / 477 (1.68%)	
occurrences causally related to treatment / all	0 / 0	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage Intracranial			
subjects affected / exposed	0 / 2 (0.00%)	7 / 477 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	5 / 477 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Infarction			
subjects affected / exposed	0 / 2 (0.00%)	5 / 477 (1.05%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	0 / 2 (0.00%)	5 / 477 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological Decompensation			
subjects affected / exposed	0 / 2 (0.00%)	4 / 477 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraventricular Haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Ischaemia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain Oedema			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed Level Of Consciousness			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial Venous Sinus Thrombosis			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			

subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered State Of Consciousness			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal Ganglia Haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basilar Artery Thrombosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid Artery Aneurysm			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain Compression			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar Ischaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar Infarction			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Haematoma			

subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Ventricle Dilatation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic Stroke			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial Paresis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic Stroke			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			

subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peroneal Nerve Palsy			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Slow Response To Stimuli			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status Epilepticus			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid Haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
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	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heparin-Induced Thrombocytopenia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic Anaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			

subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute Abdomen			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestinal Haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
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 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Ischaemic Hepatitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
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	0 / 2 (0.00%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Retention			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal Pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 2 (0.00%)	20 / 477 (4.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 2 (0.00%)	7 / 477 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	0 / 2 (0.00%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	0 / 2 (0.00%)	4 / 477 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cellulitis			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 2 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CNS Ventriculitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye Infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant Site Infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
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	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serratia Bacteraemia			

subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal Sepsis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Sepsis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural Empyema			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy Infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			

subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic Syndrome			
subjects affected / exposed	0 / 2 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Andexanet - Additional Participants	Andexanet	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	48 / 477 (10.06%)	
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	0 / 2 (0.00%)	48 / 477 (10.06%)	
occurrences (all)	0	48	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2015	• Modified the primary efficacy objective and primary efficacy end point to include changes in anti-fXa activity. The 2 primary efficacy end points were to be tested sequentially, with the proportion achieving hemostatic efficacy tested only if the change in anti-fXa activity was first demonstrated. • Modified the secondary efficacy objective and secondary efficacy end point to assess the relationship between the 2 primary efficacy end points: to evaluate the relationship between change from baseline to the evaluation period in anti-fXa activity and effective hemostasis. • Eliminated the original Study Day 1, 24-hour study data point and updated time points to Day 1, 8-hour and Day 1, 12-hour data points. • Clarified the requirements, inclusion, and exclusion criteria regarding acute major bleeding. • Changed the definition of history prior to Screening from 1 month to 2 weeks. • Modified follow-up to include rescue therapy for participants with a poor or no response. • Provided specific detail on the measurement of closed bleeds to document hemostatic control. • Increased the number of sites allowed in North America and Europe from 60 to 120.
07 May 2015	• Modified the duration of safety follow-up from 45 to 30 days to align follow-up period with standard clinical practice for intracranial hemorrhage recovery timelines. • Clarified that (visible) bleeding must be overt to qualify for inclusion in this trial. • Clarified that intracranial hemorrhage bleeds could be diagnosed and assessed with either computed tomography or magnetic resonance imaging. • Included edoxaban as 1 of the FXa inhibitors that could qualify a participant for this trial. Also, clarified that the list of FXa inhibitors being studied in this study was restricted to apixaban, edoxaban, rivaroxaban, and enoxaparin. • Clarified that participants who were scheduled for surgery to occur within the first 12 hours after receiving andexanet should not be enrolled in this study. • Clarified the blood and blood-related products were allowed as well as the time frames allowed. • Increased the size of allowable hematoma volume from 30 to 60 cubic centimetres to enable the participant population to be more representative of what might be expected in the clinical setting. • Shortened and/or consolidated the restrictions around duration of prior exposure to medications to within 7 days of andexanet treatment, based on expected duration of effect. • Provided specificity around rating of hemostatic efficacy for different subtypes of intracranial hemorrhage.

06 January 2017	• Increased sample size from 250 participants to 350 participants. • Enriched participant population for intracranial hemorrhage; ensured a minimum of 110 efficacy evaluable intracranial hemorrhage participants, including 50 participants at high risk for hematoma expansion. • Added a requirement for a reasonable expectation that a participant would be treated with andexanet within 2 hours after a baseline scan (intracranial hemorrhage participants only). • Excluded participants with visible, intra-articular, and musculoskeletal bleeding. • Excluded participants for whom the Investigator believed that the hemoglobin would drop below 8 grams/decilitre after volume resuscitation. • Changed threshold of efficacy evaluability for enoxaparin participants from 0.5 to 0.25 international units/millilitre (IU/mL). • Added clinical criteria for re-bleeding and guidance for re-dosing of andexanet in the event of re-bleeding. • Added re-bleeding, tissue factor pathway inhibitor (TFPI), antithrombin III, anti-IIa activity, Glasgow Coma Scale, Modified Rankin Score, and National Institutes of Health Stroke Scale as exploratory efficacy end points. • Converted thrombin generation from a safety end point to an efficacy end point, and mortality from an efficacy end point to a safety end point. • Added additional time points through 72 hours post-andexanet dosing for TFPI levels and thrombin generation. • Updated andexanet dosing recommendations.
02 July 2018	• To establish lower anti-fXa activity threshold for participants taking edoxaban to reflect contemporary understanding of risks and benefits of edoxaban. • Efficacy evaluable participants was re-defined as follows: All patients must have a central laboratory-determined anti-fXa activity ≥ 75 ng/mL for patients receiving apixaban and rivaroxaban, ≥ 40 ng/mL for patients receiving edoxaban, and ≥ 0.25 IU/mL for patients receiving enoxaparin. All other criteria stayed the same. • Exclusion criterion #5 was updated as follows: The patient has a recent history (within 2 weeks) of a diagnosed TE as follows: Venous Thromboembolism (VTE; e.g., deep venous thrombosis, PE, cerebral venous thrombosis), MI (including an isolated troponin elevation), DIC, cerebral vascular accident, TIA, unstable angina pectoris hospitalization, or severe peripheral vascular disease within 2 weeks prior to Screening (see Protocol Amendment 5, Appendix E for DIC scoring algorithm). • Clarified definition of re-bleeding to be consistent throughout protocol. • Updated and clarified investigational product return and destruction.
30 November 2018	• Corrected an error in the Synopsis and updated for accuracy and to align with the protocol body. • Clarified that adverse events and survival was to be followed through the study. • Updated to simplify the description of the study periods related to safety monitoring. • As a surrogate for elevated anti-fXa activity, the eligibility criteria restrict enrollment to participants who received their last dose of FXa inhibitor within 18 hours, if the timing is known. (If the timing of the last dose of FXa inhibitor is unknown, the andexanet bolus must begin as soon as possible–following signing of the informed consent form [ICF] and completion of pretreatment procedures–but no later than 3 hours following signing of the ICF). • Clarified exclusion criterion 4.2 to include language about the timing of additional surgery (12 hours after end of andexanet infusion). • Updated the andexanet dosing to reflect accurate ranges of < 30 mg (low dose) and ≥ 30 mg (high dose) for andexanet dosing in participants receiving edoxaban. • Added the Sponsor in Japan as Bristol-Myers Squibb K.K. in collaboration with Portola Pharmaceuticals, Inc. • Eliminated or revised all sentences related to enoxaparin participants because the dose of enoxaparin allowed in the study was not approved in Japan. • Modified andexanet dosing regimen for each FXa inhibitor. • Revised sentences related to drug supply and accountability from managing by Portola Pharmaceuticals, Inc. to managing by Bristol-Myers Squibb K.K. • Increased sample size to 500 participants to ensure adequate enrollment of various subgroups within the enrolled population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27573206

http://www.ncbi.nlm.nih.gov/pubmed/28009495

http://www.ncbi.nlm.nih.gov/pubmed/30730782