Clinical trial results:
A Randomized Clinical Trial of Andexanet Alfa in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor

Summary

EudraCT number	2018-002620-17
Trial protocol	FR DE GB AT BE NL ES GR CZ LV FI NO LT PL PT DK IT HU
Global end of trial date	09 August 2023

Results information

Result version number	v1 (current)
This version publication date	15 August 2024
First version publication date	15 August 2024

Trial information

Trial identification

Sponsor protocol code	18-513

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03661528
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals, Inc.
Sponsor organisation address	121 Seaport Boulevard, Boston, MA, United States,
Public contact	European Clinical Trial Information, Alexion Pharmaceuticals, Inc., +35 3874162507, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Pharmaceuticals, Inc., +35 3874162507, 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	09 August 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to evaluate the effect of andexanet versus usual care on the rate of effective hemostasis.

Protection of trial subjects:

This study was performed in accordance with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable International Council for Harmonisation/GCP guidelines, and applicable laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 June 2019
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	Canada: 28
Country: Number of subjects enrolled	United States: 28
Country: Number of subjects enrolled	Germany: 186
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Italy: 35
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Israel: 30
Country: Number of subjects enrolled	Austria: 29
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	Netherlands: 24
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Czechia: 4

Country: Number of subjects enrolled	Latvia: 4
Country: Number of subjects enrolled	Lithuania: 3
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Sweden: 2
Worldwide total number of subjects	530
EEA total number of subjects	425

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)	33
From 65 to 84 years	349
85 years and over	148

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Data collected for the Andexanet Alfa arm were prespecified to be collected as a single Arm/Group regardless of the dose level the participant received.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Arms

Are arms mutually exclusive?	Yes
Arm title	Andexanet Alfa

Arm description:

Participants received a regimen of andexanet alfa administered as an intravenous (IV) bolus, immediately followed by a continuous infusion. Dosing regimen was based on which FXa inhibitor the participants received and the amount and timing of the most recent dose of treatment.

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

Dosage and administration details:

Andexanet was received per dosage and administration details specified in the arm description.

Arm title	Usual Care

Arm description:

Participants received usual care. Usual care consisted of any treatment(s) (including no treatment) other than andexanet alfa administered within 3 hours post-randomization that the Investigator and/or other treating physicians considered to be appropriate.

Arm type	Active comparator
Investigational medicinal product name	Usual care
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Usual care was received per dosage and administration details specified in the arm description.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This is a randomized, open-label study with blinded adjudication on primary efficacy and safety outcomes, including death and thrombotic events.

Number of subjects in period 1	Andexanet Alfa	Usual Care
Started	263	267
Received at Least 1 Dose of Study Drug	262	265
Completed	180	193
Not completed	83	74
Adverse event, serious fatal	1	-
Physician decision	3	1
Consent withdrawn by subject	5	3
Adverse event, non-fatal	61	55
Other than Specified	5	2
Disease Progression	8	13

Baseline characteristics

Reporting groups	
Reporting group title	Andexanet Alfa
Reporting group description:	
Participants received a regimen of andexanet alfa administered as an intravenous (IV) bolus, immediately followed by a continuous infusion. Dosing regimen was based on which FXa inhibitor the participants received and the amount and timing of the most recent dose of treatment.	
Reporting group title	Usual Care
Reporting group description:	
Participants received usual care. Usual care consisted of any treatment(s) (including no treatment) other than andexanet alfa administered within 3 hours post-randomization that the Investigator and/or other treating physicians considered to be appropriate.	

Reporting group values	Andexanet Alfa	Usual Care	Total
Number of subjects	263	267	530
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)	15	18	33
From 65-84 years	171	178	349
85 years and over	77	71	148
Age Continuous Units: years			
arithmetic mean	79.4	78.7	
standard deviation	± 8.51	± 8.61	-
Sex: Female, Male Units: participants			
Female	117	128	245
Male	146	139	285
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	4	7
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	5	4	9
White	239	247	486
More than one race	0	0	0
Unknown or Not Reported	16	12	28
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	15	13	28
Not Hispanic or Latino	227	237	464

Unknown or Not Reported	21	17	38

End points

End points reporting groups

Reporting group title	Andexanet Alfa

Reporting group description:

Participants received a regimen of andexanet alfa administered as an intravenous (IV) bolus, immediately followed by a continuous infusion. Dosing regimen was based on which FXa inhibitor the participants received and the amount and timing of the most recent dose of treatment.

Reporting group title	Usual Care

Reporting group description:

Participants received usual care. Usual care consisted of any treatment(s) (including no treatment) other than andexanet alfa administered within 3 hours post-randomization that the Investigator and/or other treating physicians considered to be appropriate.

Primary: Number of Participants who Achieved Effective Hemostasis

End point title	Number of Participants who Achieved Effective Hemostasis

End point description:

Effective hemostasis was defined as change from baseline in National Institutes of Health Stroke Scale (NIHSS) of +6 or less at 12 hour timepoint and ≤35% increase in haematoma volume compared to baseline on a repeat computed tomography (CT) or magnetic resonance imaging (MRI) scan at 12 hours and no rescue therapies between 3-12 hours after randomization (defined as excellent or good hemostasis). The NIHSS is a validated quantitative assessment tool to measure stroke-related neurological deficits and ranges from 0 (no deficits) to 42 (very severe impairment). Data presented is number of participants with effective hemostasis (excellent or good hemostasis) adjudicated by the independent Endpoint Adjudication Committee (IEAC). Measured in the Intent-to-Treat Population (ITT), primary efficacy population, which included all participants randomized to treatment based on first data cut-off. Number of participants analyzed = participants evaluable for the endpoint.

End point type	Primary

End point timeframe:

Baseline up to 12 hours

End point values	Andexanet Alfa	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	228		
Units: participants	150	121		

Statistical analyses

Statistical analysis title	Andexanet Alfa vs Usual Care
Comparison groups	Andexanet Alfa v Usual Care

Number of subjects included in analysis	452
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0032
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage proportion difference
Point estimate	13.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.6
upper limit	22.2

Secondary: Percentage Change from Baseline to Nadir in Anti-FXa Activity

End point title	Percentage Change from Baseline to Nadir in Anti-FXa Activity

End point description:

Anti-FXa activity was measured from plasma samples to assess the anticoagulant status of FXa inhibitors using a modified chromogenic assay performed at a Central Laboratory. Nadir was defined as the minimum anti-FXa activity post-randomization. Measured in the ITT set, primary efficacy population, which included all participants randomized to study intervention based on the first data cut-off. Here, 'Overall number of participants analyzed' = participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to 2 hours

End point values	Andexanet Alfa	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	199		
Units: Percent change				
median (full range (min-max))	-94.41 (-99.1 to 1805.0)	-27.46 (-97.9 to 416.0)		

Statistical analyses

Statistical analysis title	Andexanet Alfa vs Usual Care
Comparison groups	Andexanet Alfa v Usual Care
Number of subjects included in analysis	402
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS mean based on ranks
Point estimate	-185.99

Confidence interval	
level	95 %
sides	2-sided
lower limit	-199.93
upper limit	-172.05

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 30 days

Adverse event reporting additional description:

Data are presented for randomized participants who received treatment and were analyzed according to treatment received. All cause mortality includes deaths due to AEs, initial intracranial hemorrhage, or participants who discontinued and died on, or after, the day of discontinuation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Usual Care

Reporting group description:

Participants received usual care. Usual care consisted of any treatment(s) (including no treatment) other than andexanet alfa administered within 3 hours post-randomization that the Investigator and/or other treating physicians considered to be appropriate.

Reporting group title	Andexanet Alfa

Reporting group description:

Participants received a regimen of andexanet alfa administered as an IV bolus, immediately followed by a continuous infusion. Dosing regimen was based on which FXa inhibitor the participants received and the amount and timing of the most recent dose of treatment.

Serious adverse events	Usual Care	Andexanet Alfa	
Total subjects affected by serious adverse events			
subjects affected / exposed	96 / 265 (36.23%)	120 / 262 (45.80%)	
number of deaths (all causes)	70	74	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	2 / 265 (0.75%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain cancer metastatic			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial occlusive disease			

subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 265 (0.38%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 265 (0.75%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery embolism			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism arterial			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
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 / 265 (0.00%)	1 / 262 (0.38%)	
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 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 265 (0.38%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sudden cardiac death			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory arrest			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	7 / 265 (2.64%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	2 / 7	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Respiratory failure			
subjects affected / exposed	4 / 265 (1.51%)	4 / 262 (1.53%)	
occurrences causally related to treatment / all	0 / 4	1 / 4	
deaths causally related to treatment / all	0 / 4	1 / 4	
Acute respiratory failure			

subjects affected / exposed	1 / 265 (0.38%)	3 / 262 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			
subjects affected / exposed	1 / 265 (0.38%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary oedema			
subjects affected / exposed	0 / 265 (0.00%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress			
subjects affected / exposed	0 / 265 (0.00%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
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 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			

subjects affected / exposed	3 / 265 (1.13%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Brain herniation			
subjects affected / exposed	2 / 265 (0.75%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Subdural haematoma			
subjects affected / exposed	2 / 265 (0.75%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt thrombosis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
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	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute cardiac event			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 265 (0.00%)	3 / 262 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Acute myocardial infarction			
subjects affected / exposed	2 / 265 (0.75%)	3 / 262 (1.15%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 265 (0.38%)	8 / 262 (3.05%)	
occurrences causally related to treatment / all	0 / 1	7 / 8	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac arrest			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (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	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sinus node dysfunction			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure chronic			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac dysfunction			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (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			
Haemorrhage intracranial			

subjects affected / exposed	11 / 265 (4.15%)	8 / 262 (3.05%)	
occurrences causally related to treatment / all	1 / 11	0 / 8	
deaths causally related to treatment / all	0 / 4	0 / 5	
Cerebral haemorrhage			
subjects affected / exposed	11 / 265 (4.15%)	7 / 262 (2.67%)	
occurrences causally related to treatment / all	0 / 11	0 / 7	
deaths causally related to treatment / all	0 / 9	0 / 6	
Ischaemic stroke			
subjects affected / exposed	2 / 265 (0.75%)	13 / 262 (4.96%)	
occurrences causally related to treatment / all	0 / 2	10 / 13	
deaths causally related to treatment / all	0 / 0	0 / 3	
Hydrocephalus			
subjects affected / exposed	4 / 265 (1.51%)	7 / 262 (2.67%)	
occurrences causally related to treatment / all	0 / 4	1 / 7	
deaths causally related to treatment / all	0 / 1	0 / 2	
Neurological decompensation			
subjects affected / exposed	7 / 265 (2.64%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cerebral haematoma			
subjects affected / exposed	5 / 265 (1.89%)	3 / 262 (1.15%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Epilepsy			
subjects affected / exposed	2 / 265 (0.75%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 265 (0.38%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	2 / 265 (0.75%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cerebrospinal fluid circulation disorder			
subjects affected / exposed	1 / 265 (0.38%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	2 / 265 (0.75%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Somnolence			
subjects affected / exposed	1 / 265 (0.38%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar stroke			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral vasoconstriction			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral venous thrombosis			

subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbance in attention			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic transformation stroke			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intracranial haematoma			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intraventricular haemorrhage			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorder			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Seizure			

subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke in evolution			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subdural hygroma			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
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 / 265 (0.00%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	1 / 265 (0.38%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 265 (0.00%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			

subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal mass			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic enteritis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 265 (0.00%)	3 / 262 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			

subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder rupture			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	16 / 265 (6.04%)	14 / 262 (5.34%)	
occurrences causally related to treatment / all	0 / 16	0 / 14	
deaths causally related to treatment / all	0 / 6	0 / 7	
Pneumonia aspiration			
subjects affected / exposed	7 / 265 (2.64%)	14 / 262 (5.34%)	
occurrences causally related to treatment / all	0 / 7	0 / 14	
deaths causally related to treatment / all	0 / 5	0 / 7	
Sepsis			
subjects affected / exposed	2 / 265 (0.75%)	6 / 262 (2.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 3	
Urinary tract infection			
subjects affected / exposed	1 / 265 (0.38%)	4 / 262 (1.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 265 (0.38%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
COVID-19			

subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
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	1 / 265 (0.38%)	0 / 262 (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	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			

subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 265 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Failure to thrive			
subjects affected / exposed	1 / 265 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Usual Care	Andexanet Alfa	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	200 / 265 (75.47%)	198 / 262 (75.57%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 265 (7.17%)	18 / 262 (6.87%)	
occurrences (all)	19	18	
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 265 (7.17%)	24 / 262 (9.16%)	
occurrences (all)	19	24	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	22 / 265 (8.30%)	23 / 262 (8.78%)	
occurrences (all)	23	24	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	25 / 265 (9.43%)	39 / 262 (14.89%)	
occurrences (all)	25	40	
Nausea			

subjects affected / exposed	17 / 265 (6.42%)	23 / 262 (8.78%)	
occurrences (all)	17	24	
Vomiting			
subjects affected / exposed	14 / 265 (5.28%)	9 / 262 (3.44%)	
occurrences (all)	14	9	
Psychiatric disorders			
Delirium			
subjects affected / exposed	26 / 265 (9.81%)	20 / 262 (7.63%)	
occurrences (all)	26	20	
Insomnia			
subjects affected / exposed	9 / 265 (3.40%)	14 / 262 (5.34%)	
occurrences (all)	10	14	
Infections and infestations			
Pneumonia			
subjects affected / exposed	25 / 265 (9.43%)	28 / 262 (10.69%)	
occurrences (all)	26	30	
Pneumonia aspiration			
subjects affected / exposed	16 / 265 (6.04%)	19 / 262 (7.25%)	
occurrences (all)	17	19	
Urinary tract infection			
subjects affected / exposed	44 / 265 (16.60%)	54 / 262 (20.61%)	
occurrences (all)	44	59	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	28 / 265 (10.57%)	40 / 262 (15.27%)	
occurrences (all)	28	42	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2020	- Inclusion/exclusion criteria revised - Objectives updated - Added section to clarify the population on which the primary and secondary endpoints were to be analyzed - Sample size increased from ~ 440 to ~ 900 participants and number of investigational sites from ~ 100 to ~ 200. - Added stratification factors of intended-usual-care-agent and time from symptom onset to baseline imaging scan, and removed stratification by site, to the randomization scheme.
29 July 2021	- Inclusion/exclusion criteria updated - The secondary efficacy objective related to percent change from baseline to nadir in anti-FXa activity was changed from 3 to 2 h post randomization. - Clarified use of hemostatic agents, procoagulant blood products, and other unplanned rescue procedures and surgeries within 3 h post randomization and adjudication by the Endpoint Adjudication Committee (EAC) - Added study-specific exceptions to AE and serious AE reporting - Updated instructions for reporting clinically significant laboratory abnormalities as AEs - Clarified scope of adjudication of primary endpoint by the EAC. - AE reporting revised. - Addition of section on potential risks to study participants posed by the coronavirus disease 2019 (COVID-19) pandemic.
01 December 2022	- Removal of enoxaparin eligible population (that had been added in CSP Amendment 2) based on Sponsor decision. - Deleted "stratification factor of intended-usual-care-agent." from analyses. - Interim analysis stopping criteria based on primary efficacy endpoint were clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported