Clinical trial results:
Prospective, Open-Label Clinical Study of Andexanet Alfa in Patients Receiving FXa (Activated Factor X) Inhibitor Who Require Urgent Surgery

Summary

EudraCT number	2020-000374-21
Trial protocol	DE AT
Global end of trial date	25 January 2022

Results information

Result version number	v2 (current)
This version publication date	07 June 2023
First version publication date	15 December 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	ALXN2070-19-515

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals, Inc.
Sponsor organisation address	100 College Street, New Haven, CT, United States, 06510
Public contact	Alexion Europe SAS European Clinical Trial Information, Alexion Pharmaceuticals, Inc., +33 7 87148158, clinicaltrials@alexion.com
Scientific contact	Alexion Europe SAS European Clinical Trial Information, Alexion Pharmaceuticals, Inc., +33 7 87148158, clinicaltrials@alexion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	
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	30 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 November 2021
Global end of trial reached?	Yes
Global end of trial date	25 January 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Prospective, open-label clinical trial to evaluate the efficacy and safety of andexanet alfa participants who require urgent surgery that have been anticoagulated with the FXa (activated factor X) inhibitors.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (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	27 June 2021
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	United States: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	10
EEA total number of subjects	9

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)	0
From 65 to 84 years	10

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants who required urgent surgery and received factor Xa (fXa) inhibitors (apixaban, rivaroxaban, edoxaban, or enoxaparin) before surgery were enrolled in the study.

Pre-assignment

Screening details:

This study is a single-arm study and all participants received 1 of 2 doses of andexanet based on the specific anticoagulant taken. All data were prespecified to be collected as a single Arm/Group for any participant who received at least 1 dose of the study drug, regardless of their dose level.

Period 1

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

Arms

Arm title	Andexanet Alfa

Arm description:

Participants received a dose of andexanet alfa based on the specific FXa inhibitor, dose, and time since the last dose (<8 hours, ≥8 hours, or unknown).

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

Dosage and administration details:

Participants received Andexanet Alfa at prespecified dose and timepoints.

Number of subjects in period 1	Andexanet Alfa
Started	10
Treated with any Amount of Andexanet	10
Efficacy Set	6
Completed	5
Not completed	5
Adverse event, serious fatal	5

Baseline characteristics

Reporting groups	
Reporting group title	Andexanet Alfa
Reporting group description:	
Participants received a dose of andexanet alfa based on the specific FXa inhibitor, dose, and time since the last dose (<8 hours, ≥8 hours, or unknown).	

Reporting group values	Andexanet Alfa	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	10	10	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	79.8		
full range (min-max)	68 to 84	-	
Sex: Female, Male Units: Participants			
Female	7	7	
Male	3	3	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	6	6	
More than one race	0	0	
Unknown or Not Reported	4	4	
Ethnicity (NIH/OMB)			
Per local law, ethnicity data not collected for participants located in France.			
Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	6	6	
Unknown or Not Reported	4	4	

End points

End points reporting groups

Reporting group title	Andexanet Alfa

Reporting group description:

Participants received a dose of andexanet alfa based on the specific FXa inhibitor, dose, and time since the last dose (<8 hours, ≥8 hours, or unknown).

Primary: Number of Participants Achieving Effective Hemostasis

End point title	Number of Participants Achieving Effective Hemostasis[1]

End point description:

Effective hemostasis is defined as excellent or good as assessed by the Investigator; Ineffective hemostasis is defined as moderate or poor as assessed by the Investigator. Efficacy Set: Participants who underwent surgery and had a baseline anti-fXa activity of at least 75 nanograms (ng)/milliliter (mL) for participants receiving apixaban or rivaroxaban, 40 ng/mL for participants receiving edoxaban, and 0.25 international units (IU)/mL for participants on enoxaparin. All data were prespecified to be collected as a single Arm/Group for any participant who received at least 1 dose of the study drug, regardless of their dose level.

End point type	Primary

End point timeframe:

Hemostasis will be assessed from the start of surgery to the end of the procedure.

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: Endpoint was summarized descriptively.

End point values	Andexanet Alfa			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Participants	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline In Anti-fXa Activity To Treatment Nadir

End point title	Percent Change From Baseline In Anti-fXa Activity To Treatment Nadir

End point description:

Baseline is defined as the last non-missing value on or before first study drug administration. On treatment nadir is the minimum value of anti-fXa activity during the period of time from the end of the andexanet bolus to the end of the andexanet infusion. Efficacy Set: Participants who underwent surgery and had a baseline anti-fXa activity of at least 75 ng/mL for participants receiving apixaban or rivaroxaban, 40 ng/mL for participants receiving edoxaban, and 0.25 IU/mL for participants on enoxaparin. All data were prespecified to be collected as a single Arm/Group for any participant who received at least 1 dose of the study drug, regardless of their dose level.

End point type	Secondary

End point timeframe:

Baseline, Treatment nadir (not to exceed a total of 6.5 hours of andexanet dosing)

End point values	Andexanet Alfa			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Percent Change				
median (full range (min-max))	-96.13 (-97.4 to -89.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Day 37

Adverse event reporting additional description:

All data were prespecified to be collected as a single Arm/Group for any participant who received at least 1 dose of the study drug, regardless of their dose level.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Andexanet Alfa

Reporting group description:

Participants received a dose of andexanet alfa based on the specific FXa inhibitor, dose, and time since the last dose (<8 hours, ≥8 hours, or unknown).

Serious adverse events	Andexanet Alfa		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Periprosthetic fracture			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postprocedural hematoma			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Cardiac disorders			

Stress cardiomyopathy			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Respiratory, thoracic and mediastinal disorders			
Respiratory arrest			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Andexanet Alfa		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Vitamin D deficiency			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Vitamin B complex deficiency			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 September 2019	Significant changes incorporated to this global amendment included: • Added more exploratory endpoints: - Relationship between hemostatic ecacy and anti fXa activity - Length of time from clinical presentation at the treating facility to the start of surgery - Time hospitalized in a post anesthesia care unit (PACU), assessed at the Day 30 visit - Time in the operating room (OR) • Clarified timing of FXa dosing in relation to surgery to allow enrollment of participants who received their last dose of a FXa inhibitor >15 hours before surgery if their anti fXa activity level is >100 ng/milliliter mL (or >0.5 IU/mL for participants taking enoxaparin) within 2 hours of consent • Clarified criteria for re-dosing and extended infusion • Clarified that only participants with eective levels of anticoagulation will be included in the ecacy analysis population • Updated eligibility criteria to exclude participants who have - acute overt bleeding that is potentially life threatening - overt bleeding associated with a fall in hemoglobin level by ≥ 2 grams (g)/deciliter (dL) or a hemoglobin level of ≤8 g/dL if no baseline hemoglobin is available - acute bleeding in a critical area or organ - a nonsurgical interventional procedure as the primary procedure of ecacy assessment - heparin-induced thrombocytopenia (with or without thrombosis) - inherited coagulopathy - last dose of apixaban <2.5 mg, rivaroxaban <10 mg, edoxaban <30 mg, or enoxaparin 40 mg • Increased sample size to account for possible attrition rates and rare events • Removed null and alternative hypotheses testing • Added 'physical examination' and 'centrally adjudicated' deaths to the safety assessments and clarified that all safety analyses will be performed in Safety Analysis Population
19 November 2019	Significant changes incorporated to this global amendment included: • Revised study phase from Phase 3 to Phase 2 • Added that participants will be closely monitored during the period where they are most vulnerable, and the risk of thrombosis is highest • Added allowance of 2.5 mg of apixaban • Updated eligibility criteria to exclude participants who have - Known hypersensitivity to any component of andexanet - Known allergic reaction to hamster proteins - Known or suspected (that is, presumed positive) COVID-19 related illness at the time of Screening • Clarified the section on informed consent to include acknowledgement that proxy consents must be permissible by national regulatory authorities and that emergency consent is not permitted • Reduced the sample size from 200 participants to 100 participants to align with goals for a Phase 2 study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated early due to the limited value as a single-arm study.

Notes: