Clinical trial results:
A Phase 1, Open-label, Single-dose, Non-randomized Study to Evaluate Pharmacokinetics, Pharmacodynamics, and Safety of Betrixaban in Pediatric Patients

Summary

EudraCT number	2018-002562-40
Trial protocol	GB
Global end of trial date	08 October 2019

Results information

Result version number	v1
This version publication date	30 April 2021
First version publication date	30 April 2021

Trial information

Trial identification

Sponsor protocol code	16-021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03346083
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Portola Pharmaceuticals, LLC, a wholly owned subsidiary of Alexion Pharmaceuticals, Inc.
Sponsor organisation address	121 Seaport Boulevard, Boston, MA, United States, 02210
Public contact	European Clinical Trial Information, Alexion Europe SAS, +33 14710615, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Europe SAS, +33 14710615, clinicaltrials.eu@alexion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001834-PIP02-16
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	08 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 October 2019
Global end of trial reached?	Yes
Global end of trial date	08 October 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This trial was a Phase 1, open-label, multicenter study of the pharmacokinetics (PK), pharmacodynamics (PD), and safety of a single dose of betrixaban in pediatric participants at risk of venous thromboembolism (VTE). This study was to be conducted in 2 parts: Part 1 and Part 2. Part 1 (the initial opening of the study) was conducted in 21 adolescent participants (12 to < 18 years of age) who were assessed to be at risk for VTE. Participants in Part 1 received either 40 or 80 milligrams (mg) of study drug. The PK and PD data from Part 1 was to be used for dose determination for the next youngest age group using population PK and physiological-based PK modeling and simulation. Following analysis of Part 1 data, Part 2 of the study was to commence and enroll 12 participants 2 to < 12 years of age. However, after completion of Part 1 and prior to initiating Part 2, the Sponsor decided to cease developing betrixaban, prompting early study closure.

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	14 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Russian Federation: 14
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Ukraine: 2
Worldwide total number of subjects	21
EEA total number of subjects	0

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)	21
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After a screening period of up to 30 days, eligible participants who had provided assent and for whom a parent or legal guardian had provided signed informed consent entered the hospital, clinical research unit, or Phase 1 unit on Day -1. Those who were already inpatients remained hospitalized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Betrixaban 40 mg

Arm description:

Participants received a single, oral dose of betrixaban at 40 mg in a fed state, and had 10 PK blood sampling time points.

Arm type	Experimental
Investigational medicinal product name	Betrixaban
Investigational medicinal product code	
Other name	PRT054021
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Betrixaban was administered as a single oral dose of 40 mg.

Arm title	Cohort 2: Betrixaban 80 mg

Arm description:

Participants received a single, oral dose of betrixaban at 80 mg in a fed state, and had 5 PK sampling time points.

Arm type	Experimental
Investigational medicinal product name	Betrixaban
Investigational medicinal product code	
Other name	PRT054021
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Betrixaban was administered as a single oral dose of 80 mg.

Number of subjects in period 1	Cohort 1: Betrixaban 40 mg	Cohort 2: Betrixaban 80 mg
Started	3	18
Received At Least 1 Dose Of Study Drug	3	18
Evaluated Through Day 7 Follow-up	3	18
Completed	3	18

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Betrixaban 40 mg
Reporting group description:	
Participants received a single, oral dose of betrixaban at 40 mg in a fed state, and had 10 PK blood sampling time points.	
Reporting group title	Cohort 2: Betrixaban 80 mg
Reporting group description:	
Participants received a single, oral dose of betrixaban at 80 mg in a fed state, and had 5 PK sampling time points.	

Reporting group values	Cohort 1: Betrixaban 40 mg	Cohort 2: Betrixaban 80 mg	Total
Number of subjects	3	18	21
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)	3	18	21
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	2	9	11
Male	1	9	10
Race Units: Subjects			
White	3	15	18
Black or African American	0	2	2
Other	0	1	1
Ethnicity Units: Subjects			
Not Hispanic or Latino	3	17	20
Hispanic or Latino	0	0	0
Unknown	0	1	1

End points

End points reporting groups

Reporting group title	Cohort 1: Betrixaban 40 mg
Reporting group description:	
Participants received a single, oral dose of betrixaban at 40 mg in a fed state, and had 10 PK blood sampling time points.	
Reporting group title	Cohort 2: Betrixaban 80 mg
Reporting group description:	
Participants received a single, oral dose of betrixaban at 80 mg in a fed state, and had 5 PK sampling time points.	

Primary: Area Under The Plasma Concentration–time Curve From 0 To Infinity (AUC(0-inf)) Of Betrixaban

End point title	Area Under The Plasma Concentration–time Curve From 0 To Infinity (AUC(0-inf)) Of Betrixaban[1]
End point description:	
The AUC(0-inf) of betrixaban was to be reported in mg/litre/hour (mg/L/h). Following the Sponsor's decision to cease developing betrixaban, PK parameters were not calculated.	
End point type	Primary
End point timeframe:	
Up to 6 days post dose	

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: Following the Sponsor's decision to cease developing betrixaban, statistical analysis of PK parameters was not performed.

End point values	Cohort 1: Betrixaban 40 mg	Cohort 2: Betrixaban 80 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: mg/L/h				
arithmetic mean (standard deviation)	()	()		

Notes:

[2] - Following the Sponsor's decision to cease developing betrixaban, PK parameters were not calculated.
[3] - Following the Sponsor's decision to cease developing betrixaban, PK parameters were not calculated.

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Plasma Concentration (Cmax) Of Betrixaban

End point title	Maximum Observed Plasma Concentration (Cmax) Of Betrixaban[4]
End point description:	
The Cmax of betrixaban was to be reported in mg/L. Following the Sponsor's decision to cease developing betrixaban, PK parameters were not calculated.	
End point type	Primary

End point timeframe:

Up to 6 days post dose

Notes:

[4] - 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: Following the Sponsor’s decision to cease developing betrixaban, statistical analysis of PK parameters was not performed.

End point values	Cohort 1: Betrixaban 40 mg	Cohort 2: Betrixaban 80 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: mg/L				
arithmetic mean (standard deviation)	()	()		

Notes:

[5] - Following the Sponsor’s decision to cease developing betrixaban, PK parameters were not calculated.
[6] - Following the Sponsor’s decision to cease developing betrixaban, PK parameters were not calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: AUC To The Last Measurable Concentration Above The Quantitation Limit (AUC(0-last)) Of Betrixaban

End point title	AUC To The Last Measurable Concentration Above The Quantitation Limit (AUC(0-last)) Of Betrixaban

End point description:

The AUC(0-last) of betrixaban was to be reported in mg/L/h. Following the Sponsor’s decision to cease developing betrixaban, PK parameters were not calculated.

End point type	Secondary

End point timeframe:

Up to 6 days post dose

End point values	Cohort 1: Betrixaban 40 mg	Cohort 2: Betrixaban 80 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: mg/L/h				
arithmetic mean (standard deviation)	()	()		

Notes:

[7] - Following the Sponsor’s decision to cease developing betrixaban, PK parameters were not calculated.
[8] - Following the Sponsor’s decision to cease developing betrixaban, PK parameters were not calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Plasma Half-life (t½) Of Betrixaban

End point title	Terminal Plasma Half-life (t½) Of Betrixaban

End point description:

The t½ of betrixaban was to be reported in h. Following the Sponsor’s decision to cease developing betrixaban, PK parameters were not calculated.

End point type	Secondary

End point timeframe:

Up to 6 days post dose

End point values	Cohort 1: Betrixaban 40 mg	Cohort 2: Betrixaban 80 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: hour				
arithmetic mean (standard deviation)	()	()		

Notes:

[9] - Following the Sponsor’s decision to cease developing betrixaban, PK parameters were not calculated.
[10] - Following the Sponsor’s decision to cease developing betrixaban, PK parameters were not calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Time To Maximum Observed Plasma Concentration (Tmax) Of Betrixaban

End point title	Time To Maximum Observed Plasma Concentration (Tmax) Of Betrixaban

End point description:

The Tmax of betrixaban was to be reported in h. Following the Sponsor’s decision to cease developing betrixaban, PK parameters were not calculated.

End point type	Secondary

End point timeframe:

Up to 6 days post dose

End point values	Cohort 1: Betrixaban 40 mg	Cohort 2: Betrixaban 80 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: hour				
arithmetic mean (standard deviation)	()	()		

Notes:

[11] - Following the Sponsor’s decision to cease developing betrixaban, PK parameters were not calculated.
[12] - Following the Sponsor’s decision to cease developing betrixaban, PK parameters were not calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Total Body Clearance Of Betrixaban From Plasma (CL)

End point title	Apparent Total Body Clearance Of Betrixaban From Plasma (CL)

End point description:

The CL of betrixaban was to be reported in mg/h. Following the Sponsor's decision to cease developing betrixaban, PK parameters were not calculated.

End point type	Secondary

End point timeframe:

Up to 6 days post dose

End point values	Cohort 1: Betrixaban 40 mg	Cohort 2: Betrixaban 80 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: mg/h				
arithmetic mean (standard deviation)	()	()		

Notes:

[13] - Following the Sponsor's decision to cease developing betrixaban, PK parameters were not calculated.
[14] - Following the Sponsor's decision to cease developing betrixaban, PK parameters were not calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume Of Distribution (Vd) Of Betrixaban

End point title	Apparent Volume Of Distribution (Vd) Of Betrixaban

End point description:

The Vd of betrixaban was to be reported in L/kilogram (kg). Following the Sponsor's decision to cease developing betrixaban, PK parameters were not calculated.

End point type	Secondary

End point timeframe:

Up to 6 days post dose

End point values	Cohort 1: Betrixaban 40 mg	Cohort 2: Betrixaban 80 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[15]	0[16]		
Units: L/kg				
arithmetic mean (standard deviation)	()	()		

Notes:

[15] - Following the Sponsor's decision to cease developing betrixaban, PK parameters were not calculated.
[16] - Following the Sponsor's decision to cease developing betrixaban, PK parameters were not

calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline In Thrombin Level At Day 6

End point title	Percent Change From Baseline In Thrombin Level At Day 6

End point description:

Following the Sponsor’s decision to cease developing betrixaban, PD parameters were not calculated.

End point type	Secondary

End point timeframe:

Baseline, Day 6

End point values	Cohort 1: Betrixaban 40 mg	Cohort 2: Betrixaban 80 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[17]	0[18]		
Units: percent				
arithmetic mean (standard deviation)	()	()		

Notes:

[17] - Following the Sponsor’s decision to cease developing betrixaban, PD parameters were not calculated.

[18] - Following the Sponsor’s decision to cease developing betrixaban, PD parameters were not calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Number Of Participants With Treatment-related Adverse Events

End point title	Number Of Participants With Treatment-related Adverse Events

End point description:

A treatment-related adverse event was any undesirable event or any untoward medical occurrence that occurs to a participant during the course of a study, or the protocol-defined time after study termination. An Investigator qualified in medicine made the determination of relationship to the investigational product for each adverse event (Unrelated, Unlikely Related, Possibly Related, or Probably Related). If the relationship between the adverse event and the investigational product was determined to be “possible” or “probable”, the event was considered to be related to the investigational product for the purposes of expedited regulatory reporting. One participant experienced a mild study-drug-related headache that resolved in less than 2 hours. A summary of serious and all other non-serious adverse events, regardless of causality, is located in the Reported Adverse Events module.

End point type	Secondary

End point timeframe:

Up to 7 days post dose

End point values	Cohort 1: Betrixaban 40 mg	Cohort 2: Betrixaban 80 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	18		
Units: Participants	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 7 days post dose.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Cohort 1: Betrixaban 40 mg
Reporting group description: Participants received a single, oral dose of betrixaban at 40 mg in a fed state, and had 10 PK blood sampling time points.	
Reporting group title	Cohort 2: Betrixaban 80 mg
Reporting group description: Participants received a single, oral dose of betrixaban at 80 mg in a fed state, and had 5 PK sampling time points.	

Serious adverse events	Cohort 1: Betrixaban 40 mg	Cohort 2: Betrixaban 80 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 18 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort 1: Betrixaban 40 mg	Cohort 2: Betrixaban 80 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	5 / 18 (27.78%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Cardiac disorders			

Bradycardia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 18 (5.56%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 18 (5.56%) 1	
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0	1 / 18 (5.56%) 1 1 / 18 (5.56%) 1	
Infections and infestations Sinusitis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 18 (5.56%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2017	1. Redundantly emphasized protocol requirement for a subsequent protocol amendment and ethics approval prior to the commencement of Part 2 (ages 2–12 years) and again prior to the commencement of Part 3 (ages 28 days to 2 years) to specify age appropriate blood sampling volumes and time points following review of data from the previous age cohorts. It is intended that a reduction of blood sampling time points and therefore volumes will be possible during the study of progressively younger age groups by selecting the most informative time points based on data review. 2. Provided additional guidance to minimize pain and discomfort to pediatric participants during blood sampling. Sampling may occur via intravenous catheter or butterfly needle followed by saline flush. For participants with pre-existing central venous catheter or access devices (that is, central line, central venous line, or central venous access catheter) sampling may occur via these access points.
06 April 2018	1. Reduced size of Cohort 1 (40 mg) from 12 participants to 3 participants. Cohort 1 will serve as the single cohort containing 10 PK time points per participant. This rich sampling schedule will serve as the basis for bridging to pediatric PK from adult PK. To minimize the number of participants subjected to a rich sampling schedule, Cohort 2 (80 mg) will employ a sparse sampling schedule consisting of 5 PK time points per participant that will be combined to compile a complete average plasma concentration time course. The overall reduction of sampling time points is intended to minimize pain and discomfort to pediatric participants. Part 1 of the study will now consist of: - Cohort 1: Single dose, 40 mg, fed (n=3), rich PK sampling - Cohort 2: Single dose, 80 mg, fed (n=18), sparse PK sampling Following review of safety data from Cohort 1 (40 mg), the Sponsor may authorize continued enrollment into Cohort 2 (80 mg). 2. Reduced the number of PK sampling from 10 to 5 blood sampling time points to minimize pain and discomfort to pediatric participants. Participants in Cohort 2 will be assigned 1 of 3 blood sampling sequences. In aggregate, sequences will cover the majority of PK sampling time points. PK sampling sequences are described as: - Sequence A: predose, 1, 3, 12, and 120 h post-dose - Sequence B: predose, 0.5, 2, 4, and 24 h post-dose - Sequence C: predose, 2, 3, 12, and 24 h post-dose 3. Removed the study of the youngest age group (28 days to 2 years old) from this protocol, which was previously referred to as Part 3 of the 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.

After completion of Part 1 and prior to initiating Part 2, the Sponsor decided to cease developing betrixaban, prompting early study closure.

Notes: