Clinical trial results:
apixaban in end -stage renal disease

Summary

EudraCT number	2015-003132-12
Trial protocol	BE
Global end of trial date	24 August 2018

Results information

Result version number	v1 (current)
This version publication date	03 January 2021
First version publication date	03 January 2021

Trial information

Trial identification

Sponsor protocol code	s57150

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03456648
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UZ Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Bjorn Meijers, UZ Leuven, 32 16342409, bjorn.meijers@uzleuven.be
Scientific contact	Bjorn Meijers, UZ Leuven, 32 16342409, bjorn.meijers@uzleuven.be

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 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 August 2018
Global end of trial reached?	Yes
Global end of trial date	24 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

to determine inter-dialytic pharmacokinetics of Apixaban

Protection of trial subjects:

Patients were under direct supervision of a (para-)medic during the first 24 hours after administration of the IMP

Background therapy:

Maintenance hemodialysis (hemodiafiltration not allowed) three times/ week
During study period regional citrate anticoagulation with a calcium-containing dialysate was used

Evidence for comparator: -

Actual start date of recruitment	09 September 2016
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	Belgium: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	12
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients treated with maintenance hemodialysis by the dialysis unit of the university hospitals Leuven. Patients were recruited between 09-09-2016 and 12-04-2018

Pre-assignment

Screening details:

Inclusion criteria
- Patients aged 18 to 85 years
- Maintenance (dialysis vintage >3 months) thrice weekly hemodialysis

Exclusion criteria
- Treated with oral vitamin K antagonists
- Recent (< 4 weeks prior to informed consent) major surgery
- Recent (< 4 weeks prior to informed cons severe bleeding episode requiring blood transfusion

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	High Dose predialysis

Arm description:

apixaban 5 mg pre-dialysis

Arm type	Experimental
Investigational medicinal product name	apixaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Apixaban 5 mg

Arm title	low dose predialysis

Arm description:

Apixaban 2.5 mg pre-dialysis

Arm type	Experimental
Investigational medicinal product name	apixaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Apixaban 2.5 mg

Arm title	High dose post-dialysis

Arm description:

Apixaban 5 mg post-dialysis

Arm type	Experimental

Investigational medicinal product name	apixaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Apixaban 5 mg taken after the hemodialysis session

Arm title	Low dose post-dialysis

Arm description:

Apixaban 2.5 mg post-dialysis

Arm type	Experimental
Investigational medicinal product name	apixaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Apixaban 2.5 mg

Number of subjects in period 1	High Dose predialysis	low dose predialysis	High dose post-dialysis
Started	6	6	6
Completed	6	6	6

Number of subjects in period 1	Low dose post-dialysis
Started	6
Completed	6

Baseline characteristics

Reporting groups	
Reporting group title	High Dose predialysis
Reporting group description: apixaban 5 mg pre-dialysis	
Reporting group title	low dose predialysis
Reporting group description: Apixaban 2.5 mg pre-dialysis	
Reporting group title	High dose post-dialysis
Reporting group description: Apixaban 5 mg post-dialysis	
Reporting group title	Low dose post-dialysis
Reporting group description: Apixaban 2.5 mg post-dialysis	

Reporting group values	High Dose predialysis	low dose predialysis	High dose post-dialysis
Number of subjects	6	6	6
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	71.7	59.3	72.8
full range (min-max)	63 to 85	33 to 85	66 to 84
Gender categorical Units: Subjects			
Female	2	1	3
Male	4	5	3

Reporting group values	Low dose post-dialysis	Total	
Number of subjects	6	24	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	70.5		
full range (min-max)	64 to 77	-	
Gender categorical			
Units: Subjects			
Female	4	10	
Male	2	14	

End points

End points reporting groups	
Reporting group title	High Dose predialysis
Reporting group description: apixaban 5 mg pre-dialysis	
Reporting group title	low dose predialysis
Reporting group description: Apixaban 2.5 mg pre-dialysis	
Reporting group title	High dose post-dialysis
Reporting group description: Apixaban 5 mg post-dialysis	
Reporting group title	Low dose post-dialysis
Reporting group description: Apixaban 2.5 mg post-dialysis	

Primary: AUC (0-48h)	
End point title	AUC (0-48h)
End point description: Area under the curve (AUC) from intake until 48 hours after intake	
End point type	Primary
End point timeframe: Single dose AUC 0-48 h	

End point values	High Dose predialysis	low dose predialysis	High dose post-dialysis	Low dose post-dialysis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: ng/mL/h				
median (full range (min-max))	2792.1 (1750 to 3788)	1159 (563 to 1938)	3817.6 (1243 to 5604)	2214.2 (479 to 4411)

Statistical analyses

Statistical analysis title	overall difference AUC
Statistical analysis description: Kruskall-Wallis (non-parametric ANOVA)	
Comparison groups	High Dose predialysis v low dose predialysis v High dose post-dialysis v Low dose post-dialysis

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0186 [2]
Method	ANOVA
Parameter estimate	Kruskall-Wallis distribution of variance
Point estimate	0.019
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.011
upper limit	0.026
Variability estimate	Standard deviation
Dispersion value	0.008

Notes:

[1] - Kruskall-Wallis (non-parametric ANOVA)

[2] - overall difference

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 30 days after administration of IMP	
Assessment type	Systematic

Dictionary used	
Dictionary name	ICD
Dictionary version	9

Reporting groups	
Reporting group title	High Dose predialysis
Reporting group description: apixaban 5 mg pre-dialysis	
Reporting group title	low dose predialysis
Reporting group description: Apixaban 2.5 mg pre-dialysis	
Reporting group title	High dose post-dialysis
Reporting group description: Apixaban 5 mg post-dialysis	
Reporting group title	Low dose post-dialysis
Reporting group description: Apixaban 2.5 mg post-dialysis	

Serious adverse events	High Dose predialysis	low dose predialysis	High dose post-dialysis
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Hepatobiliary disorders			
Liver function test increased	Additional description: subacute liver failure		
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection	Additional description: severe upper respiratory tract infection requiring hospitalization		
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Inflammation	Additional description: inflammation requiring hospitalization		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Low dose post-dialysis		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Hepatobiliary disorders			
Liver function test increased	Additional description: subacute liver failure		
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection	Additional description: severe upper respiratory tract infection requiring hospitalization		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Inflammation	Additional description: inflammation requiring hospitalization		
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	High Dose predialysis	low dose predialysis	High dose post-dialysis
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
Hepatobiliary disorders			
liver function test abnormal	Additional description: Mild elevation of liver function tests		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Low dose post-dialysis		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)		
Hepatobiliary disorders			
liver function test abnormal	Additional description: Mild elevation of liver function tests		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

Single centre, single dose pharmacodynamics study

Notes: