Clinical trial results:
Multiple-Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Apixaban in Pediatric Subjects with an Indwelling Central Venous Catheter

Summary

EudraCT number	2010-024597-19
Trial protocol	BE NL Outside EU/EEA
Global end of trial date	05 October 2012

Results information

Result version number	v1
This version publication date	06 January 2017
First version publication date	06 January 2017

Trial information

Trial identification

Sponsor protocol code	CV185-079

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01195727
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb, clinical.trials@bms.com
Scientific contact	EU Study Start-Up Unit, Bristol-Myers Squibb, clinical.trials@bms.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000183-PIP01-08, EMEA-000183-PIP02-12
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 October 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 October 2012
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is primarily to study the pharmacokinetics and pharmacodynamics of Apixaban in pediatric subjects with a central venous cathether.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	19 July 2011
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: 12
Country: Number of subjects enrolled	Mexico: 1
Worldwide total number of subjects	13
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)	2
Adolescents (12-17 years)	11
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:

A total of 13 subjects were enrolled, and 8 received study treatment. 5 subjects were enrolled but not treated due to screen failures.

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	4A (0.60 mg/m2 Apixaban)

Arm description:

Subjects were administered 0.60 mg/m2 Apixaban, twice daily (every 12 hours with a +/- 1 hour window), for 10 days (Day 1 through Day 10).

Arm type	Experimental
Investigational medicinal product name	Apixaban
Investigational medicinal product code	
Other name	Eliquis
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Apixaban oral solution (0.4 mg/mL) was administered twice daily for 10 days.

Arm title	5A (0.66 mg/m2 Apixaban)

Arm description:

Subjects were administered 0.66 mg/m2 Apixaban, twice daily (every 12 hours with a +/- 1 hour window), for 10 days (Day 1 through Day 10).

Arm type	Experimental
Investigational medicinal product name	Apixaban
Investigational medicinal product code	
Other name	Eliquis
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Apixaban oral solution (0.4 mg/mL) was administered by mouth via graduated dosing syringe, twice daily, for 10 days.

Number of subjects in period 1[1]	4A (0.60 mg/m2 Apixaban)	5A (0.66 mg/m2 Apixaban)
Started	2	6
Completed	1	5
Not completed	1	1
Poor/noncompliance	1	-
Adverse event, non-fatal	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Of the 13 subjects enrolled, only 8 received treatment.

Baseline characteristics

Reporting groups	
Reporting group title	4A (0.60 mg/m2 Apixaban)
Reporting group description:	
Subjects were administered 0.60 mg/m2 Apixaban, twice daily (every 12 hours with a +/- 1 hour window), for 10 days (Day 1 through Day 10).	
Reporting group title	5A (0.66 mg/m2 Apixaban)
Reporting group description:	
Subjects were administered 0.66 mg/m2 Apixaban, twice daily (every 12 hours with a +/- 1 hour window), for 10 days (Day 1 through Day 10).	

Reporting group values	4A (0.60 mg/m2 Apixaban)	5A (0.66 mg/m2 Apixaban)	Total
Number of subjects	2	6	8
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)	2	0	2
Adolescents (12-17 years)	0	6	6
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	8.5	15.7	
standard deviation	± 3.54	± 1.75	-
Gender categorical			
Units: Subjects			
Female	2	0	2
Male	0	6	6

End points

End points reporting groups

Reporting group title	4A (0.60 mg/m2 Apixaban)
Reporting group description:	
Subjects were administered 0.60 mg/m2 Apixaban, twice daily (every 12 hours with a +/- 1 hour window), for 10 days (Day 1 through Day 10).	
Reporting group title	5A (0.66 mg/m2 Apixaban)
Reporting group description:	
Subjects were administered 0.66 mg/m2 Apixaban, twice daily (every 12 hours with a +/- 1 hour window), for 10 days (Day 1 through Day 10).	

Primary: Geometric Mean of Model-Estimated Individual Steady-State Cmax Parameters

End point title	Geometric Mean of Model-Estimated Individual Steady-State Cmax Parameters[1]
End point description:	
A Population Pharmacokinetics (PPK) model was developed using plasma apixaban concentration versus time data. Maximum estimated plasma concentration at steady state (Cmax) in each subject was derived from model-estimated population and individual PK parameters (eg: CL/F, Vc/F, KA). Geometric means were reported in nanograms per milliliter (ng/mL) along with the coefficient of variation (%CV). All treated subjects were included in the analysis.	
End point type	Primary
End point timeframe:	
Apixaban concentrations were collected at 9 time points from Days 1 through 11.	
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: Only summary statistics were planned for this endpoint	

End point values	4A (0.60 mg/m2 Apixaban)	5A (0.66 mg/m2 Apixaban)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	6		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	32.99 (± 41.4)	32.94 (± 34.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean of Model-Estimated Steady-State AUC(TAU) of Apixaban

End point title	Geometric Mean of Model-Estimated Steady-State AUC(TAU) of Apixaban[2]
End point description:	
A Population Pharmacokinetics (PPK) model was developed using plasma apixaban concentration versus time data. Model-estimated population and individual PK parameters (eg: CL/F, Vc/F, KA) were used to derive the steady-state estimated area under the plasma concentration time curve for one dosing	

interval [AUC(TAU)] in each subject. Geometric means were reported in nanogram hours per milliliter (ng*hr/mL) along with the coefficient of variation (%CV). All treated subjects were included in the analysis.

End point type	Primary

End point timeframe:

Apixaban concentrations were collected at 9 time points from Days 1 through 11.

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: Only summary statistics were planned for this endpoint

End point values	4A (0.60 mg/m2 Apixaban)	5A (0.66 mg/m2 Apixaban)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	6		
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)	223.5 (± 29.4)	234.6 (± 32.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean of Model-Estimated Individual Steady-State Cmin parameters

End point title	Geometric Mean of Model-Estimated Individual Steady-State Cmin parameters[3]

End point description:

A Population Pharmacokinetics (PPK) model was developed using plasma apixaban concentration versus time data. Minimum estimated plasma concentration at steady state (Cmin) in each subject was derived from model-estimated population and individual PK parameters (eg: CL/F, Vc/F, KA) . Geometric means were reported in nanograms per milliliter (ng/mL) along with the coefficient of variation (%CV). All treated subjects were included in the analysis.

End point type	Primary

End point timeframe:

Apixaban concentrations were collected at 9 time points from Days 1 through 11.

Notes:

[3] - 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: Only summary statistics were planned for this endpoint

End point values	4A (0.60 mg/m2 Apixaban)	5A (0.66 mg/m2 Apixaban)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	6		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	8.63 (± 33.7)	10.19 (± 47)		

Statistical analyses

No statistical analyses for this end point

Primary: Median Time to Model-Estimated Steady-State Plasma Concentration Maximum (Tmax)

End point title	Median Time to Model-Estimated Steady-State Plasma Concentration Maximum (Tmax)[4]

End point description:

A population PK (PPK) model was developed using plasma apixaban concentration versus time data. Model-estimated population and individual PK parameters (eg. CL/F, Vc/F, KA) were used to derive time to maximum steady-state concentration (Tmax) of Apixaban in each subject. Medians were reported in hours post-dose at steady state. All treated subjects were included in the analysis.

End point type	Primary

End point timeframe:

Apixaban concentrations were collected at 9 time points from Days 1 through 11.

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: Only summary statistics were planned for this endpoint

End point values	4A (0.60 mg/m2 Apixaban)	5A (0.66 mg/m2 Apixaban)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	6		
Units: hours				
median (full range (min-max))	1.45 (1 to 1.9)	1.5 (1 to 2.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Absorption Rate (Ka) of Apixaban

End point title	Geometric Mean Absorption Rate (Ka) of Apixaban[5]

End point description:

The absorption rate was defined as the rate at which Apixaban entered the blood stream. A population PK (PPK) model was developed using plasma apixaban concentration versus time data. Subject PK parameter values were derived using a nonlinear mixed-effects ("population") compartmental model. Geometric means for the individual estimated absorption rate (Ka) parameters were presented in (1/h) along with the coefficient of variation (%CV). All treated subjects were included in the analysis.

End point type	Primary

End point timeframe:

Apixaban concentrations were collected at 9 time points from Days 1 through 11.

Notes:

[5] - 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: Only summary statistics were planned for this endpoint

End point values	4A (0.60 mg/m2 Apixaban)	5A (0.66 mg/m2 Apixaban)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	6		
Units: 1/h				
geometric mean (geometric coefficient of variation)	1.37 (± 63.8)	1.21 (± 56.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean of Apparent Plasma Clearance Rate (CL/F) of Apixaban

End point title	Geometric Mean of Apparent Plasma Clearance Rate (CL/F) of Apixaban[6]

End point description:

Apparent plasma clearance after extravascular administration (CL/F) of Apixaban was estimated for each subject. A population PK (PPK) model was developed using plasma apixaban concentration versus time data. Subject PK parameter values were derived using a nonlinear mixed-effects ("population") compartmental model. Geometric means for the individual estimated apparent oral clearance (CL/F) parameters were presented in (L/h) along with the coefficient of variation (%CV). All treated subjects were included in the analysis.

End point type	Primary

End point timeframe:

Apixaban concentrations were collected at 9 time points from Days 1 through 11.

Notes:

[6] - 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: Only summary statistics were planned for this endpoint

End point values	4A (0.60 mg/m2 Apixaban)	5A (0.66 mg/m2 Apixaban)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	6		
Units: L/h				
geometric mean (geometric coefficient of variation)	2.82 (± 10.8)	4.86 (± 33.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric mean of apparent volume of distribution of the central compartment (Vc/F)

End point title	Geometric mean of apparent volume of distribution of the central compartment (Vc/F)[7]

End point description:

A population PK (PPK) model was developed using plasma apixaban concentration versus time data. Subject PK parameter values were derived using a nonlinear mixed-effects ("population")

compartmental model. Geometric means for the individual estimated apparent volume of distribution of the central compartment (Vc/F) were presented in liters along with the coefficient of variation (%CV). All treated subjects were included in the analysis.

End point type	Primary

End point timeframe:

Apixaban concentrations were collected at 9 time points from Days 1 through 11.

Notes:

[7] - 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: Only summary statistics were planned for this endpoint

End point values	4A (0.60 mg/m2 Apixaban)	5A (0.66 mg/m2 Apixaban)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	6		
Units: liters				
geometric mean (geometric coefficient of variation)	15.99 (± 6.2)	30.03 (± 29.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean maximum estimated anti-Xa activity at steady state (AXAmax)

End point title	Mean maximum estimated anti-Xa activity at steady state (AXAmax)

End point description:

A Population Pharmacokinetic-Pharmacodynamic (PPK-PD) model was developed for anti-FXa activity vs. apixaban concentration and used to estimate the maximum anti-FXa activity at steady state (AXAmax). Means were reported in Low Molecular Weight Heparin activity units (IU/mL). All treated subjects were included in the analysis.

End point type	Secondary

End point timeframe:

Blood draws for anti-Xa activity were performed at 6 time points from Days 1 through 7.

End point values	4A (0.60 mg/m2 Apixaban)	5A (0.66 mg/m2 Apixaban)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	6		
Units: IU/mL				
arithmetic mean (standard deviation)	0.5835 (± 0.2425)	0.583 (± 0.1984)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean minimum estimated anti-Xa activity at steady state (AXAmin)

End point title	Mean minimum estimated anti-Xa activity at steady state (AXAmin)

End point description:

A Population Pharmacokinetic-Pharmacodynamic (PPK-PD) model was developed for anti-FXa activity vs. apixaban concentration and used to estimate the minimum anti-FXa activity at steady state (AXAmin). Means are reported in Low Molecular Weight Heparin activity units (IU/mL). All treated subjects were included in the analysis.

End point type	Secondary

End point timeframe:

Blood draws for anti-Xa activity were performed at 6 time points from Days 1 through 7.

End point values	4A (0.60 mg/m2 Apixaban)	5A (0.66 mg/m2 Apixaban)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	6		
Units: IU/mL				
arithmetic mean (standard deviation)	0.1495 (± 0.0502)	0.1875 (± 0.0883)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose to 90 days after last dose	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	4A (0.60 mg/m2 Apixaban)
Reporting group description:	
Subjects were administered 0.60 mg/m2 Apixaban, twice daily (every 12 hours with a +/- 1 hour window), for 10 days (Day 1 through Day 10).	
Reporting group title	5A (0.66 mg/m2 Apixaban)
Reporting group description:	
Subjects were administered 0.66 mg/m2 Apixaban, twice daily (every 12 hours with a +/- 1 hour window), for 10 days (Day 1 through Day 10).	

Serious adverse events	4A (0.60 mg/m2 Apixaban)	5A (0.66 mg/m2 Apixaban)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sinusitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
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	4A (0.60 mg/m2 Apixaban)	5A (0.66 mg/m2 Apixaban)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	3 / 6 (50.00%)	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 2 (50.00%)	3 / 6 (50.00%)	
occurrences (all)	1	3	
Blood creatinine increased			
subjects affected / exposed	1 / 2 (50.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Blood urea decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
International normalised ratio increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Lymphocyte count decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Lymphocyte count increased			
subjects affected / exposed	1 / 2 (50.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 2 (50.00%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Infections and infestations			
Periorbital cellulitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1	0 / 6 (0.00%) 0	
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 August 2010	The main purpose of this amendment is to update the enrollment scheme to state that data from 3 subjects in Group 2B is reviewed prior to enrolling neonates in Group 1. In addition, updates have been made in regard to prohibited and restricted use of treatments and provide additional supporting information to the rational pertaining to the enrollment of neonates.
27 December 2010	The main purpose of this amendment is to update the stopping rules for individual subject discontinuation as well as criteria for when the study would be terminated. Other updates include the addition of language that the sponsor in conjunction with the investigators will review data at selected milestones throughout the study; the addition of recommended treatment guidelines for bleeding or suspected bleeding events, and language to allow dose adjustments to be implemented on the morning of Day 3.
11 December 2011	The main purpose of this amendment is to update the Exclusion Criteria relating to positive urine screen for drugs of abuse for adolescents allowing medical monitor approval; allowance of concomitant medications during the study; Remove need for duplicate PD sample on Day 1, 0 hour, deletion of the statement that plasma samples will be archived for potential metabolite analysis; deletion of the statement that subjects who receive placebo in any panel will be pooled into a single placebo group. Other updates include a change of the Study Directors and editorial updates.
25 June 2012	The main purpose of this amendment is to update the Study Design section, whereas only Adolescents 12 years to <18 years (Cohorts 5A & 5B) will continue to be enrolled in the study. Due to slow recruitment rate of younger age groups enrollment of subjects younger than 12 years was terminated after two (2) subjects from Cohort 4A were enrolled (Age Group 6 years to <12 years; Dose: 0.60 mg/m2). The number of total subjects in the study will change from 60 to 12 (from Cohorts 5A & 5B). Reference to any other Cohorts, in the study design, has been removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 October 2012	Due to difficulties in recruiting pediatric subjects, this study was amended to limit recruitment to adolescent subjects (12 to <18 years of age), and then subsequently terminated prior to completion of the adolescent group.	-

Notes:

Limitations and caveats

None reported