Clinical trial results:
An Open Label, Non-Randomised, Phase IV Clinical Trial to Determine the Transfer of Apixaban and Rivaroxaban in Breast Milk Following Oral Administration

Summary

EudraCT number	2018-003852-19
Trial protocol	GB
Global end of trial date	07 March 2020

Results information

Result version number	v1 (current)
This version publication date	28 March 2021
First version publication date	28 March 2021
Summary attachment (see zip file)	Clinical Study report (Clinical Study Report v1.0 Final signed.pdf)

Trial information

Trial identification

Sponsor protocol code	DOAC

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Roopen Arya, King's College London, +44 02032993570, roopen.arya@nhs.net
Scientific contact	Roopen Arya, King's College London, +44 02032993570, roopen.arya@nhs.net
Sponsor organisation name	King's College Hospital NHS Foundation Trust
Sponsor organisation address	Denmark Hill, London, United Kingdom, SE5 9RS
Public contact	Roopen Arya, King's college Hospital NHS Foundation Trust, +44 02032993570, roopen.arya@nhs.net
Scientific contact	Roopen Arya, King's college Hospital NHS Foundation Trust, +44 02032993570, roopen.arya@nhs.net

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	15 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 March 2020
Global end of trial reached?	Yes
Global end of trial date	07 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine if apixaban and rivaroxaban are excreted in breastmilk following single dose oral administration to breastfeeding mothers.

Protection of trial subjects:

Subjects had the right to withdraw from the study at any time for any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 January 2020
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: 3
Worldwide total number of subjects	3
EEA total number of subjects	3

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)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Potential study subjects were invited to participate in this trial via multiple routes, such as advertisements post on websites, and invitation letters enclosed with PIS sent to those women who had delivered their babies at King's College Hospital NHS Foundation Trust in the preceding year, and had been administrated LMWH during pregnancy.

Pre-assignment

Screening details:

The assessment included participant's age, duration of gestation, date of delivery, feeding regimen (exclusive breastfeeding or mixed feeding), smoking history, alcohol history, medical history, ongoing medication, blood pressure, and pulse. Laboratory tests were performed,including haematology tests,biochemistry tests,pregnancy test, and serology.

Period 1

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

Blinding implementation details:

Open label

Arms

Are arms mutually exclusive?	Yes
Arm title	Apixaban

Arm description:

5 mg of Apixaban (Eliquis®)(twice daily)

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

Dosage and administration details:

Single dose of 5 mg (twice daily).

Arm title	Rivaroxaban

Arm description:

Rivaroxaban 20mg (once daily)

Arm type	Experimental
Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	
Other name	Xarelto
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single dose of 20mg (once daily)

Number of subjects in period 1	Apixaban	Rivaroxaban
Started	1	2
Completed	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Apixaban
Reporting group description: 5 mg of Apixaban (Eliquis®)(twice daily)	
Reporting group title	Rivaroxaban
Reporting group description: Rivaroxaban 20mg (once daily)	

Reporting group values	Apixaban	Rivaroxaban	Total
Number of subjects	1	2	3
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)	1	2	3
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	1	2	3
Male	0	0	0

End points

End points reporting groups

Reporting group title	Apixaban
Reporting group description:	
5 mg of Apixaban (Eliquis®)(twice daily)	
Reporting group title	Rivaroxaban
Reporting group description:	
Rivaroxaban 20mg (once daily)	

Primary: Concentration in milk

End point title	Concentration in milk[1][2]
End point description:	

End point type	Primary
End point timeframe:	
0 to 24 hours	

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: Due to the nature of the study, descriptive statistics will be used to analyse the data and describe the study population.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to the nature of the study, descriptive statistics will be used to analyse the data and describe the study population.

End point values	Rivaroxaban			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: ng/ml				
arithmetic mean (standard deviation)				
2.5 hours	83.29 (± 2.81)			
6 hours	51.14 (± 12.24)			
10 hours	27.47 (± 3.97)			
12 hours	19.78 (± 2.47)			
24 hours	7.09 (± 10.03)			

Statistical analyses

No statistical analyses for this end point

Primary: Concentration in milk

End point title	Concentration in milk[3][4]
End point description:	

End point type	Primary

End point timeframe:

0 to 24 hours

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: Due to the nature of the study, descriptive statistics will be used to analyse the data and describe the study population.
[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to the nature of the study, descriptive statistics will be used to analyse the data and describe the study population.

End point values	Apixaban			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: ng/ml				
number (not applicable)				
3.5 hours	229.78			
hours	108.99			
12 hours	38.18			
14 hours	219.64			
16 hours	168.98			
24 hours	48.89			

Statistical analyses

No statistical analyses for this end point

Primary: Concentration in plasma

End point title	Concentration in plasma[5][6]

End point description:

End point type	Primary

End point timeframe:

0 to 24 hours

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: Due to the nature of the study, descriptive statistics will be used to analyse the data and describe the study population.
[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to the nature of the study, descriptive statistics will be used to analyse the data and describe the study population.

End point values	Rivaroxaban			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: ng/ml				
arithmetic mean (standard deviation)				

2.5 hours	325.37 (± 51.58)			
6 hours	153.41 (± 24.57)			
10 hours	101.05 (± 26.97)			
12 hours	92.52 (± 65.29)			
24 hours	30.83 (± 26.65)			

Statistical analyses

No statistical analyses for this end point

Primary: Concentration in plasma

End point title	Concentration in plasma[7][8]

End point description:

End point type	Primary

End point timeframe:

0 to 24 hours

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: Due to the nature of the study, descriptive statistics will be used to analyse the data and describe the study population.
[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to the nature of the study, descriptive statistics will be used to analyse the data and describe the study population.

End point values	Apixaban			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: ng/ml				
number (not applicable)				
3.5 hours	77.72			
7 hours	31.89			
12 hours	14.02			
14 hours	115.34			
16 hours	66.89			
24 hours	20.50			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: AEs and SAEs will be reported from first dose until 24 hours following first dose.	
Adverse event reporting additional description: AEs listed in the SmPC do not need to be reported.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

Reporting groups	
Reporting group title	Apixaban
Reporting group description: 5 mg of Apixaban (Eliquis®)(twice daily)	
Reporting group title	Rivaroxaban
Reporting group description: Rivaroxaban 20mg (once daily)	

Serious adverse events	Apixaban	Rivaroxaban	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Apixaban	Rivaroxaban	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	0 / 2 (0.00%)	
Gastrointestinal disorders			
gum bleeding			
subjects affected / exposed	1 / 1 (100.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2019	IMP change: Dabigatran changed to Apixaban. Change occurred prior to recruitment start.

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 final subject was unable to be recruited due to the COVID-19 pandemic.

Notes: