



Clinical trial results:

Rivaroxaban in Antiphospholipid Syndrome (RAPS). A prospective randomised controlled phase II/III clinical trial of rivaroxaban versus warfarin in patients with thrombotic antiphospholipid syndrome, with or without SLE.

Summary

EudraCT number	2012-002345-38
Trial protocol	GB
Global end of trial date	08 June 2015

Results information

Result version number	v1 (current)
This version publication date	26 October 2018
First version publication date	26 October 2018

Trial information

Trial identification

Sponsor protocol code	12/0033/CTU/IMM/001
-----------------------	---------------------

Additional study identifiers

ISRCTN number	ISRCTN68222801
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Comprehensive Clinical Trials Unit at UCL
Sponsor organisation address	Institute of Clinical Trials and Methodology, 90 High Holborn, London, United Kingdom, WC1V 6LJ
Public contact	CCTU Enquiry Desk, Comprehensive Clinical Trials Unit at UCL, CCTU-enquiries@ucl.ac.uk
Scientific contact	CCTU Enquiry Desk, Comprehensive Clinical Trials Unit at UCL, CCTU-enquiries@ucl.ac.uk

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	08 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2014
Global end of trial reached?	Yes
Global end of trial date	08 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether the anticoagulant effects of rivaroxaban (established for the treatment and secondary prevention of venous thromboembolism) are not inferior to those of warfarin in patients with antiphospholipid syndrome, with or without systemic lupus erythematosus (SLE). This was measured by comparing the percentage change in endogenous thrombin potential (ETP), assessed by thrombin generation, from randomisation to day 42, with non-inferiority set at less than 20% difference from warfarin in mean percentage change. Analysis was by modified intention to treat. Other thrombin generation parameters, thrombosis, and bleeding were also assessed. Treatment effect was measured as the ratio of rivaroxaban to warfarin for thrombin generation.

Protection of trial subjects:

The trial was conducted in compliance with the approved protocol, UCL CCTU Standard Operating Procedures, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

Protocol pre-defined reasons for discontinuation of trial medication: unacceptable toxicity; unacceptable SAE; pregnancy. Protocol pre-defined reasons for possible discontinuation of trial medication: SAE; thrombotic event; any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion (included needing any drug specified in the exclusion criteria). All participants could choose to discontinue trial treatment at any time, without giving a reason, without penalty or loss of benefits to which they would otherwise be entitled.

Protocol pre-defined dose modifications were in place for patients with renal impairment – the dose of rivaroxaban could be modified if creatinine clearance decreased. Procedures were in place for treatment with rivaroxaban to be temporarily stopped if a patient had a bleeding event or needed bridging anticoagulation for a procedure (routine or emergency).

Investigation and treatment of adverse events (including bleeding) were as per NHS standard of care. All participants were asked to attend hospital and contact their trial site immediately if they experienced symptoms suggestive of recurrent thrombosis, VTE or arterial, and in the event of severe or persistent bleeding. Participants randomised to rivaroxaban were supplied with the contact details for a healthcare professional to gain information on what to do about rivaroxaban in the event of bleeding.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 June 2013
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 Kingdom: 116
--------------------------------------	---------------------

Worldwide total number of subjects	116
EEA total number of subjects	116

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)	96
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in two hospitals in England with randomisations from 05 June 2013 to 11 November 2014. Participants were randomly assigned 1:1 to continue with warfarin or receive 20 mg oral rivaroxaban daily. Randomisation was done centrally, stratified by centre and patient type (with vs without SLE).

Pre-assignment

Screening details:

Inclusion: Patients with APS, with or without SLE, who were taking warfarin for a minimum of 3mths since last VTE (whilst not on anticoagulation or recurrent episode(s) which occurred whilst off anticoagulation or on sub-therapeutic anticoagulant therapy), with a target INR of 2.5 (range 2.0 – 3.0). Female patients using adequate contraception.

Period 1

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

Blinding implementation details:

The trial was open label to ensure optimum warfarin dosing. An unblinded study was additionally necessary as should patients have experienced bleeding, it would have been important to know immediately whether they were on warfarin or rivaroxaban as the management of bleeding events differs.

Arms

Are arms mutually exclusive?	Yes
Arm title	Warfarin

Arm description:

Warfarin prescribed and dispensed in accordance with national guidance (National Patient Safety Agency Safer Practice Notice 18 [1], and British Committee for Standards in Haematology guidelines [2]) with anticoagulant monitoring undertaken by patient's usual anticoagulation clinic.

[1] National Patient Safety Agency Safer Practice Notice 18, <https://www.sps.nhs.uk/articles/npsa-alert-actions-that-can-make-oral-anticoagulant-therapy-safer-2007/>

[2] Keeling D, et al. British Committee for Standards in Haematology (BCSH) - Guidelines for General Haematology, Haemostasis and Thrombosis. Guidelines on oral anticoagulation with warfarin – fourth edition. Br J Haematol 2011; 154: 311–324.

Arm type	Active comparator
Investigational medicinal product name	Warfarin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Standard-intensity warfarin (target international normalised ratio [INR] 2.5, range 2.0-3.0) was prescribed and dispensed in accordance with national guidance (National Patient Safety Agency Safer Practice Notice 18 [1], and British Committee for Standards in Haematology Guidelines [2])

[1] National Patient Safety Agency Safer Practice Notice 18, <https://www.sps.nhs.uk/articles/npsa-alert-actions-that-can-make-oral-anticoagulant-therapy-safer-2007/>

[2] Keeling D, et al. British Committee for Standards in Haematology (BCSH) - Guidelines for General Haematology, Haemostasis and Thrombosis. Guidelines on oral anticoagulation with warfarin – fourth edition. Br J Haematol 2011; 154: 311–324.

Arm title	Rivaroxaban
------------------	-------------

Arm description:

Fixed-dose (20mg once daily; full dosage administration details below) of the anticoagulant drug Rivaroxaban.

Arm type	Experimental
Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients with creatinine clearance ≥ 50 mL/min were instructed to take a 20mg tablet orally once daily in the morning, with food to maximise absorption, for six months.

Patients with moderate renal impairment (creatinine clearance of 30 – 49 mL/min) were prescribed either one 20mg tablet or one 15mg tablet to be taken orally once daily in the morning, with food, for six months depending on local clinical care and following the Summary of Product Characteristics (SPC) [1]. If the patient was prescribed 15mg and subsequent testing showed that the patient's creatinine clearance was ≥ 50 mL/min, the patient's dose of rivaroxaban was recommended to be increased to one 20mg tablet once daily in the morning depending on local clinical care and following the SPC.

[1] 15mg and 20mg rivaroxaban (Xarelto) SPC Bayer plc (Date of last revision November 2013) obtained from the Medicines Compendium (www.medicines.org.uk)).

Number of subjects in period 1	Warfarin	Rivaroxaban
Started	59	57
Completed	55	56
Not completed	4	1
Adverse event, non-fatal	-	1
Withdrawal	2	-
Lost to follow-up	1	-
Died	1	-

Baseline characteristics

Reporting groups

Reporting group title	Warfarin
-----------------------	----------

Reporting group description:

Warfarin prescribed and dispensed in accordance with national guidance (National Patient Safety Agency Safer Practice Notice 18 [1], and British Committee for Standards in Haematology guidelines [2]) with anticoagulant monitoring undertaken by patient's usual anticoagulation clinic.

[1] National Patient Safety Agency Safer Practice Notice 18, <https://www.sps.nhs.uk/articles/npsa-alert-actions-that-can-make-oral-anticoagulant-therapy-safer-2007/>

[2] Keeling D, et al. British Committee for Standards in Haematology (BCSH) - Guidelines for General Haematology, Haemostasis and Thrombosis. Guidelines on oral anticoagulation with warfarin – fourth edition. Br J Haematol 2011; 154: 311–324.

Reporting group title	Rivaroxaban
-----------------------	-------------

Reporting group description:

Fixed-dose (20mg once daily; full dosage administration details below) of the anticoagulant drug Rivaroxaban.

Reporting group values	Warfarin	Rivaroxaban	Total
Number of subjects	59	57	116
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	50	47	
standard deviation	± 14	± 17	-
Gender categorical Units: Subjects			
Female	42	42	84
Male	17	15	32
Stratification variable - Systemic lupus erythematosus (SLE) Units: Subjects			
Yes	11	11	22
No	48	46	94
Stratification variable - site			
Site of patient recruitment and treatment.			
Units: Subjects			
University College London Hospital	25	23	48
Guy's and St Thomas' Hospitals	34	34	68

Rivaroxaban dose			
Units: Subjects			
20mg	0	55	55
15mg	0	2	2
N/A	59	0	59
Thrombotic event with no or subtherapeutic anticoagulation			
Units: Subjects			
Deep vein thrombosis	37	32	69
Pulmonary embolism	22	25	47
Previous bleeding events while taking anticoagulation			
Units: Subjects			
Major	0	0	0
Clinically relevant	4	0	4
N/A	55	57	112
aPL (Miyakis categories)			
Units: Subjects			
I (excluding triple-positive aPL)	19	16	35
I (including triple-positive aPL)	12	7	19
IIa	23	30	53
IIb	1	3	4
IIc	4	1	5
Raised in-vivo coagulation activation markers - prothrombin fragment 1.2			
Units: Subjects			
Yes	1	0	1
No	58	57	115
Raised in-vivo coagulation activation markers - Thrombin-antithrombin complex			
Units: Subjects			
Yes	2	2	4
No	57	55	112
Raised in-vivo coagulation activation markers - D-dimer			
Units: Subjects			
Yes	4	3	7
No	55	54	109
Raised in-vivo coagulation activation markers - Any marker			
Units: Subjects			
Yes	6	5	11
No	53	52	105
Laboratory data - Haemoglobin			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: g/L			
geometric mean	137	130	
standard deviation	± 1.04	± 1.06	-
Laboratory data - platelet count			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			

Units: *10(^9)/L			
geometric mean	220	222	
standard deviation	± 1.14	± 1.14	-
Laboratory data - International normalised ratio			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: ratio			
geometric mean	2.7	2.8	
standard deviation	± 1.17	± 1.10	-
Laboratory data - Creatinine clearance			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: mL/min			
geometric mean	95	92	
standard deviation	± 1.15	± 1.15	-
Laboratory data - Alanine aminotransferase			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: IU/L			
geometric mean	20	21	
standard deviation	± 1.25	± 1.22	-
Thrombin generation - ETP			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: nmol/L per min			
geometric mean	542	555	
standard deviation	± 1.28	± 1.2	-
Thrombin generation - Peak thrombin generation			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: nmol/L			
geometric mean	79.9	93.8	
standard deviation	± 1.42	± 1.34	-
In-vivo coagulation activation markers - prothrombin fragment 1.2			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: pmol/L			
geometric mean	43.1	43.3	
standard deviation	± 1.27	± 1.24	-
In-vivo coagulation activation markers - Thrombin-antithrombin complex			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: ug/L			
geometric mean	2.7	2.9	
standard deviation	± 1.10	± 1.29	-
Percentage of time in therapeutic range			

while taking warfarin Units: percentage arithmetic mean standard deviation	53 ± 24	64 ± 28	-
EQ-5D-5L Quality of life scores - Health utility Units: score arithmetic mean standard deviation	0.79 ± 0.24	0.83 ± 0.21	-
EQ-5D-5L Quality of life scores - Health state: VAS Units: score arithmetic mean standard deviation	75 ± 20	81 ± 16	-
Thrombin generation - Lag time			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: min geometric mean standard deviation	7.6 ± 1.27	7.3 ± 1.23	-
Thrombin generation - time to peak thrombin generation			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: min geometric mean standard deviation	11.7 ± 1.24	10.8 ± 1.19	-
In-vivo coagulation activation markers - D-dimer Units: mg/L Fibrinogen equivalent units (FEU) median inter-quartile range (Q1-Q3)	0.19 0.19 to 0.22	0.19 0.19 to 0.25	-

End points

End points reporting groups

Reporting group title	Warfarin
-----------------------	----------

Reporting group description:

Warfarin prescribed and dispensed in accordance with national guidance (National Patient Safety Agency Safer Practice Notice 18 [1], and British Committee for Standards in Haematology guidelines [2]) with anticoagulant monitoring undertaken by patient's usual anticoagulation clinic.

[1] National Patient Safety Agency Safer Practice Notice 18, <https://www.sps.nhs.uk/articles/npsa-alert-actions-that-can-make-oral-anticoagulant-therapy-safer-2007/>

[2] Keeling D, et al. British Committee for Standards in Haematology (BCSH) - Guidelines for General Haematology, Haemostasis and Thrombosis. Guidelines on oral anticoagulation with warfarin – fourth edition. Br J Haematol 2011; 154: 311–324.

Reporting group title	Rivaroxaban
-----------------------	-------------

Reporting group description:

Fixed-dose (20mg once daily; full dosage administration details below) of the anticoagulant drug Rivaroxaban.

Primary: ETP at day 42

End point title	ETP at day 42
-----------------	---------------

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Measurement at 42nd day after the baseline assessment at time of randomisation.

End point values	Warfarin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	54		
Units: nmol/L per min				
geometric mean (confidence interval 95%)	548 (484 to 621)	1086 (957 to 1233)		

Statistical analyses

Statistical analysis title	Primary outcome analysis
----------------------------	--------------------------

Statistical analysis description:

Linear regression was used to estimate the difference in log-ETP between the two treatments (rivaroxaban - warfarin) at day 42 together with a two-sided 95% confidence interval, adjusting for the stratification variables (site and patient type) and also baseline log-ETP. Results were then exponentiated to produce a ratio representing the difference in (geometric) mean ETP between the treatment arms (after adjustment for baseline values).

Comparison groups	Warfarin v Rivaroxaban
-------------------	------------------------

Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Regression, Linear
Parameter estimate	Ratio of geometric means
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	2.4

Secondary: Lag time at day 42

End point title	Lag time at day 42
End point description:	
End point type	Secondary
End point timeframe:	
Measurement at 42nd day after the baseline assessment at time of randomisation.	

End point values	Warfarin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	53		
Units: min				
geometric mean (confidence interval 95%)	7.3 (6.7 to 8.0)	8.9 (8.1 to 9.8)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
<p>Linear regression was used to estimate the difference in log-lag time between the two treatments (rivaroxaban - warfarin) at day 42 together with a two-sided 95% confidence interval, adjusting for the stratification variables (site and patient type) and also baseline log-lag time. Results were then exponentiated to produce a ratio representing the difference in (geometric) mean lag time between the treatment arms (after adjustment for baseline values).</p>	
Comparison groups	Warfarin v Rivaroxaban

Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0052
Method	Regression, Linear
Parameter estimate	Ratio of geometric means
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.4

Secondary: Time to peak thrombin generation at day 42

End point title	Time to peak thrombin generation at day 42
End point description:	
End point type	Secondary
End point timeframe:	
Measurement at 42nd day after the baseline assessment at time of randomisation.	

End point values	Warfarin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	54		
Units: min				
geometric mean (confidence interval 95%)	11.2 (10.3 to 12.1)	19.2 (17.7 to 20.9)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
<p>Linear regression was used to estimate the difference in log-time to peak thrombin generation between the two treatments (rivaroxaban - warfarin) at day 42 together with a two-sided 95% confidence interval, adjusting for the stratification variables (site and patient type) and also baseline log-time to peak thrombin. Results were then exponentiated to produce a ratio representing the difference in (geometric) mean time to peak between the treatment arms (after adjustment for baseline values).</p>	
Comparison groups	Warfarin v Rivaroxaban
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Linear
Parameter estimate	Ratio of geometric means
Point estimate	1.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	1.9

Secondary: Peak thrombin generation at day 42

End point title	Peak thrombin generation at day 42
End point description:	
End point type	Secondary
End point timeframe:	
Measurement at 42nd day after the baseline assessment at time of randomisation.	

End point values	Warfarin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	54		
Units: nmol/L				
geometric mean (confidence interval 95%)	85.7 (72.3 to 101.5)	55.6 (46.8 to 66.1)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Comparison groups	Rivaroxaban v Warfarin
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.00061
Method	Regression, Linear
Parameter estimate	Ratio of geometric means
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.8

Notes:

[1] - Linear regression was used to estimate the difference in log-peak thrombin generation between the two treatments (rivaroxaban - warfarin) at day 42 together with a two-sided 95% confidence interval, adjusting for the stratification variables (site and patient type) and also baseline log-peak thrombin. Results were then exponentiated to produce a ratio representing the difference in (geometric) mean peak thrombin between the treatment arms (after adjustment for baseline values).

Secondary: Prothrombin fragment 1.2 at day 42

End point title	Prothrombin fragment 1.2 at day 42
End point description:	
End point type	Secondary
End point timeframe:	
Measurement at 42nd day after the baseline assessment at time of randomisation.	

End point values	Warfarin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	57		
Units: pmol/L				
geometric mean (confidence interval 95%)	45.6 (40.1 to 52.0)	93.6 (82.1 to 106.9)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
Linear regression was used to estimate the difference in log-prothrombin fragment between the two treatments (rivaroxaban - warfarin) at day 42 together with a two-sided 95% confidence interval, adjusting for the stratification variables (site and patient type) and also baseline prothrombin values. Results were then exponentiated to produce a ratio representing the difference in (geometric) mean ETP between the treatment arms (after adjustment for baseline values).	
Comparison groups	Rivaroxaban v Warfarin
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Linear
Parameter estimate	Ratio of geometric means
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	2.5

Secondary: Thrombin–antithrombin complex at day 42

End point title	Thrombin–antithrombin complex at day 42
End point description:	
End point type	Secondary
End point timeframe:	
Measurement at 42nd day after the baseline assessment at time of randomisation.	

End point values	Warfarin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	57		
Units: ug/L				
geometric mean (confidence interval 95%)	2.6 (2.5 to 2.8)	2.4 (2.3 to 2.6)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
Linear regression was used to estimate the difference in log-thrombin-antithrombin between the two treatments (rivaroxaban - warfarin) at day 42 together with a two-sided 95% confidence interval, adjusting for the stratification variables (site and patient type) and also baseline log-thrombin-antithrombin. Results were then exponentiated to produce a ratio representing the difference in (geometric) mean thrombin-antithrombin between the treatment arms (after adjustment for baseline values).	
Comparison groups	Warfarin v Rivaroxaban
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Regression, Linear
Parameter estimate	Ratio of geometric means
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1

Secondary: D-dimer at day 42

End point title	D-dimer at day 42
End point description:	
End point type	Secondary
End point timeframe:	
Measurement at 42nd day after the baseline assessment at time of randomisation.	

End point values	Warfarin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	57		
Units: mg/L FEU				
geometric mean (confidence interval 95%)	0.19 (0.19 to 0.2)	0.19 (0.19 to 0.23)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
Linear regression was used to estimate the difference in log-D-dimer between the two treatments (rivaroxaban - warfarin) at day 42 together with a two-sided 95% confidence interval, adjusting for the stratification variables (site and patient type) and also baseline log-D-dimer. Results were then exponentiated to produce a ratio representing the difference in (geometric) mean D-dimer between the treatment arms (after adjustment for baseline values).	
Comparison groups	Warfarin v Rivaroxaban
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Regression, Linear
Parameter estimate	Ratio of geometric means
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Raised concentrations at day 42 (and also raised at baseline): prothrombin fragment 1.2 (pmol/L)

End point title	Raised concentrations at day 42 (and also raised at baseline): prothrombin fragment 1.2 (pmol/L)
End point description:	
Count of patients with raised concentrations at day 42 of follow-up, and count of those patients who also had raised concentrations at baseline.	
End point type	Secondary
End point timeframe:	
Measurement at 42nd day after the baseline assessment at time of randomisation.	

End point values	Warfarin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	57		
Units: Number of patients				
Day 42	0	2		
Baseline and day 42	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Raised concentrations at day 42 (and also raised at baseline): Thrombin-antithrombin complex (ug/L)

End point title	Raised concentrations at day 42 (and also raised at baseline): Thrombin-antithrombin complex (ug/L)
-----------------	---

End point description:

Count of patients with raised concentrations at day 42 of follow-up, and count of those patients who also had raised concentrations at baseline.

End point type	Secondary
----------------	-----------

End point timeframe:

Measurement at 42nd day after the baseline assessment at time of randomisation.

End point values	Warfarin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	57		
Units: Number of patients				
Day 42	3	0		
Baseline and day 42	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Raised concentrations at day 42 (and also raised at baseline): D-dimer (mg/L FEU)

End point title	Raised concentrations at day 42 (and also raised at baseline): D-dimer (mg/L FEU)
-----------------	---

End point description:

Count of patients with raised concentrations at day 42 of follow-up, and count of those patients who also had raised concentrations at baseline.

End point type	Secondary
----------------	-----------

End point timeframe:

Measurement at 42nd day after the baseline assessment at time of randomisation.

End point values	Warfarin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	57		
Units: Number of patients				
Day 42	4	2		
Baseline and day 42	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Raised concentrations at day 42 (and also raised at baseline): Any marker

End point title	Raised concentrations at day 42 (and also raised at baseline): Any marker
End point description:	Count of patients with raised concentrations at day 42 of follow-up, and count of those patients who also had raised concentrations at baseline.
End point type	Secondary
End point timeframe:	Measurement at 42nd day after the baseline assessment at time of randomisation.

End point values	Warfarin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	57		
Units: Number of patients				
Day 42	6	3		
Day 42 and also baseline	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Adherence at day 42: peak rivaroxaban concentration in plasma

End point title	Adherence at day 42: peak rivaroxaban concentration in plasma ^[2]
End point description:	
End point type	Secondary

End point timeframe:

Measurement at 42nd day after the baseline assessment at time of randomisation.

Notes:

[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: Not relevant for the Warfarin arm.

End point values	Rivaroxaban			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: ug/L				
median (inter-quartile range (Q1-Q3))	162 (101 to 245)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adherence at day 42: Factor X amidolytic

End point title Adherence at day 42: Factor X amidolytic^[3]

End point description:

End point type Secondary

End point timeframe:

Measurement at 42nd day after the baseline assessment at time of randomisation.

Notes:

[3] - 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: Not relevant for the Rivaroxaban arm.

End point values	Warfarin			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: IU/dL				
geometric mean (confidence interval 95%)	25.3 (23.5 to 27.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adherence at day 42: international normalised ratio

End point title Adherence at day 42: international normalised ratio^[4]

End point description:

End point type Secondary

End point timeframe:

Measurement at 42nd day after the baseline assessment at time of randomisation.

Notes:

[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: Not relevant for the Rivaroxaban arm.

End point values	Warfarin			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: ratio				
geometric mean (confidence interval 95%)	2.7 (2.6 to 2.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time between baseline and day 180 in therapeutic range

End point title	Time between baseline and day 180 in therapeutic range ^[5]
-----------------	---

End point description:

Percentage of the time between baseline and 180th day of follow-up during which the patient was in the therapeutic range for Warfarin.

End point type	Secondary
----------------	-----------

End point timeframe:

Between baseline and 180th day after the baseline assessment.

Notes:

[5] - 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: Not relevant for the Rivaroxaban arm.

End point values	Warfarin			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: percentage				
arithmetic mean (standard deviation)	55 (± 23)			

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D-5L quality of life scores at day 180: Health Utility

End point title	EQ-5D-5L quality of life scores at day 180: Health Utility
-----------------	--

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

Measurement at 180th day after the baseline assessment at time of randomisation.

End point values	Warfarin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	56		
Units: EQ-5D-5L health utility score				
arithmetic mean (standard error)	0.78 (\pm 0.02)	0.82 (\pm 0.02)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
----------------------------	----------------------------

Statistical analysis description:

Regression was used to estimate the difference in mean EQ-5D-5L Health utility between the two treatments (rivaroxaban - warfarin) at day 180 together with a two-sided 95% confidence interval, adjusting for the stratification variables (site and patient type) and also baseline EQ-5D-5L Health utility.

Comparison groups	Warfarin v Rivaroxaban
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.09

Secondary: EQ-5D-5L quality of life scores at day 180: Health state Visual Analogue Scale (VAS)

End point title	EQ-5D-5L quality of life scores at day 180: Health state Visual Analogue Scale (VAS)
-----------------	--

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

Measurement at 180th day after the baseline assessment at time of randomisation.

End point values	Warfarin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	56		
Units: EQ-5D-5L Health state VAS score				
arithmetic mean (standard error)	73 (\pm 1.8)	80 (\pm 1.8)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
Regression was used to estimate the difference in mean EQ-5D-5L Health state: VAS between the two treatments (rivaroxaban - warfarin) at day 180 together with a two-sided 95% confidence interval, adjusting for the stratification variables (site and patient type) and also baseline EQ-5D-5L Health state: VAS.	
Comparison groups	Warfarin v Rivaroxaban
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	11.5

Secondary: New thrombotic events at day 210

End point title	New thrombotic events at day 210
End point description:	
End point type	Secondary
End point timeframe:	
Measurement at 210th day after the baseline assessment at time of randomisation.	

End point values	Warfarin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	57		
Units: Number of patients				
Deep vein thrombosis	0	0		
Pulmonary embolism	0	0		
Arterial thrombosis	0	0		
Other	0	0		

Any combination	0	0		
-----------------	---	---	--	--

Statistical analyses

No statistical analyses for this end point

Secondary: Bleeding events at day 210

End point title	Bleeding events at day 210
-----------------	----------------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

Measurement at 210th day after the baseline assessment at time of randomisation.

End point values	Warfarin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	57		
Units: Number of events				
Major	0	0		
Clinically relevant	2	3		
Minor	8	10		
Unclassified, insufficient information	0	1		

Statistical analyses

Statistical analysis title	Secondary - clinically relevant bleeds comparison
----------------------------	---

Statistical analysis description:

A test for the difference between two proportions based on the normal approximation to the binomial distribution was used to estimate the difference in percentage of bleeds between the two treatments (rivaroxaban - warfarin) at day 210 together with a two-sided 95% confidence interval.

Comparison groups	Warfarin v Rivaroxaban
-------------------	------------------------

Number of subjects included in analysis	112
---	-----

Analysis specification	Pre-specified
------------------------	---------------

Analysis type	superiority
---------------	-------------

Parameter estimate	Difference between percentages
--------------------	--------------------------------

Point estimate	1.7
----------------	-----

Confidence interval	
---------------------	--

level	95 %
-------	------

sides	2-sided
-------	---------

lower limit	-5.9
-------------	------

upper limit	9.3
-------------	-----

Statistical analysis title	Secondary - minor bleeds comparison
Statistical analysis description:	
A test for the difference between two proportions based on the normal approximation to the binomial distribution was used to estimate the difference in percentage of bleeds between the two treatments (rivaroxaban - warfarin) at day 210 together with a two-sided 95% confidence interval.	
Comparison groups	Warfarin v Rivaroxaban
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference between percentages
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	16.5

Statistical analysis title	Secondary - unclassified bleeds comparison
Statistical analysis description:	
A test for the difference between two proportions based on the normal approximation to the binomial distribution was used to estimate the difference in percentage of bleeds between the two treatments (rivaroxaban - warfarin) at day 210 together with a two-sided 95% confidence interval.	
Comparison groups	Warfarin v Rivaroxaban
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference between percentages
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	5.3

Secondary: Site of bleed	
End point title	Site of bleed
End point description:	
End point type	Secondary
End point timeframe:	
Measurement at 210th day after the baseline assessment at time of randomisation.	

End point values	Warfarin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	54		
Units: Number of patients				
Intracranial	0	1		
Skin (bruise)	0	3		
Oral	1	0		
Nasal	3	5		
Vaginal	0	1		
Rectal	3	0		
Lower ureteric	0	1		
Other	7	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Measurement at 210th day after the baseline assessment at time of randomisation.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	CTCAE
-----------------	-------

Dictionary version	4
--------------------	---

Reporting groups

Reporting group title	Warfarin
-----------------------	----------

Reporting group description:

Warfarin prescribed and dispensed in accordance with national guidance (National Patient Safety Agency Safer Practice notice 18, and British Committee for Standards in Haematology guidelines) with anticoagulant monitoring undertaken by patient's usual anticoagulation clinic.

Reporting group title	Rivaroxaban
-----------------------	-------------

Reporting group description:

Fixed-dose (15mg or 20mg once daily) of the anticoagulant drug Rivaroxaban.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Adverse events were not reported for this trial, however a number was required for this field so we used the number 0 for both arms. We expect there were many adverse events in each arm. They were recorded in patient notes and used to modify NHS care, but, as per the protocol, they were not reported to sponsor unless an investigator judged they were due to the drug not working.

Serious adverse events	Warfarin	Rivaroxaban	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 55 (7.27%)	4 / 57 (7.02%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-Hodgkin's lymphoma metastatic			
subjects affected / exposed	1 / 55 (1.82%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Intracranial hemorrhage			

subjects affected / exposed	0 / 55 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	0 / 55 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhoidal hemorrhage			
subjects affected / exposed	1 / 55 (1.82%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthmatic crisis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
abdominal pain, vomiting, arthralgia, and myalgia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 57 (1.75%)	
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: 0 %

Non-serious adverse events	Warfarin	Rivaroxaban	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 55 (0.00%)	0 / 57 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2013	Protocol updated to v4.0 to include the following; the change in the SPC to SPC Mercury Pharma Group Limited 18 Sep 2012; widening of exclusion criteria to include refusal to consent to the site informing the healthcare professional responsible for anticoagulation care and those on St. John's Wort; change to inclusion criteria for treatment with warfarin now for a 3 month period not 6; arm B widened for patients with moderate renal impairment to incorporate a 20mg OD or 15mg OD depending on local clinical care or following the SPC; visit 1 time-points changed from ± 12 days to ideally -12days +14 days and all others from ideally ± 21 days to ideally ± 14 days; stopping of warfarin in patients randomised to rivaroxaban changed to on the day of conversion not the day of randomisation; the stopping of rivaroxaban being based on clinical judgment; in case any medications not permitted need to be prescribed the participant is to change to appropriate anticoagulation not 'revert back to warfarin'; Appendix C: Sections 2 and 3 made more generic as these details are covered in a SOP; clarifications throughout.
24 October 2014	Protocol updated to v5.0 to include the following: addition of in vivo coagulation activation markers to secondary outcome measures; reduction in the number randomised from 156 to 116; increase in recruitment period from 10 to 18 months and overall planned duration from 24 to 44 months; removal of measurement of abdominal circumference at screening and visit 3; classification of thrombotic events will be done by the PI not the Independent Adjudication Committee; additional exclusion criterion of patients on dronedarone; clarifications throughout.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27570089>