Clinical trial results:
RIVAROXABAN VERSUS ACENOCUMAROL EN LA PROFILAXIS SECUNDARIA DEL SÍNDROME ANTIFOSFOLÍPIDO:UN ESTUDIO MULTICÉNTRICO, PROSPECTIVO Y RANDOMIZADO.

Summary

EudraCT number	2010-019764-36
Trial protocol	ES
Global end of trial date	31 December 2014

Results information

Result version number	v1 (current)
This version publication date	16 September 2021
First version publication date	16 September 2021

Trial information

Trial identification

Sponsor protocol code	SAP-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02926170
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	VHIR
Sponsor organisation address	Passeig Vall Hebron 119-129, Barcelona, Spain, 08035
Public contact	Joaquin Lopez-Soriano, VHIR, +34 934894779, joaquin.lopez.soriano@vhir.org
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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	31 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy and safety of rivaroxaban in patients with antiphospholipid syndrome (APS), and to determine whether rivaroxaban is noninferior to dose-adjusted vitamin K antagonists (VKAs) for thrombotic APS

Protection of trial subjects:

The local ethics committees approved the study, and all participants provided written informed consent before enrollment. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles.
Adherence in the rivaroxaban group was evaluated by self-reported questionnaire.
The study treatment could be discontinued early because of unacceptable serious adverse or thrombotic events, any change in the patient's condition that justified discontinuation, consent withdrawal, pregnancy, or lack of adherence to the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 March 2013
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	Spain: 190
Worldwide total number of subjects	190
EEA total number of subjects	190

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)	155

From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult patients fulfilling the international consensus criteria for APS were recruited from internal medicine and rheumatology clinics. Eligible patients included those with objectively confirmed arterial or venous thrombosis and a positive result on aPL testing on 2 occasions at least 3 months apart. Testing for aPL was performed locally.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	190
Number of subjects completed	190

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rivaroxaban

Arm description: -

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

Dosage and administration details:

Rivaroxaban (20 mg/d, or 15 mg/d for patients with a creatinine clearance of 30 to 49 mL/min/1.73 m2

Patients were started on low molecular weight heparin (LMWH) (1 mg/kg) administered twice daily. First dose was started on the day of conversion from warfarin to rivaroxaban in the evening and continued for 48 hours. After 48 hours of LMWH, at the 3rd day of conversion, rivaroxaban 15 mg or 20 mg was started in the morning, once daily.

Patients receiving 20 mg rivaroxaban once daily could receive 15 mg if creatinine clearance changed to 30-49 mL/min, and in patients receiving 15 mg daily, the dose could be changed to 20 mg if CrCL changed to ≥50 mL/min.

Arm title	Control

Arm description: -

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

Dosage and administration details:

Adjusted dosage of VKAs s (target INR, 2.0 to 3.0, or 3.1 to 4.0 for those with a history of recurrent

thrombosis).

Number of subjects in period 1	Rivaroxaban	Control
Started	95	95
Completed	84	86
Not completed	11	9
Adverse event, serious fatal	5	3
Adverse event, non-fatal	6	6

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	190	190	
Age categorical Units: Subjects			
Adults (18-64 years)	155	155	
From 65-84 years	35	35	
Gender categorical Units: Subjects			
Female	121	121	
Male	69	69	

End points

End points reporting groups	
Reporting group title	Rivaroxaban
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	

Primary: New thrombotic events	
End point title	New thrombotic events
End point description:	
End point type	Primary
End point timeframe:	
3 years	

End point values	Rivaroxaban	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	95		
Units: percent				
number (not applicable)	11.6	6.3		

Statistical analyses

Statistical analysis title	Recurrent Thrombosis rate
Comparison groups	Rivaroxaban v Control
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.21
Method	Risk Ratio

Secondary: Time to thrombosis	
End point title	Time to thrombosis
End point description:	
End point type	Secondary
End point timeframe:	
3 years	

End point values	Rivaroxaban	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	95		
Units: units	11	6		

Statistical analyses

Statistical analysis title	Time to thrombotic event
Comparison groups	Control v Rivaroxaban
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.19
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	1.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	5.24

Secondary: Type of thrombotic event

End point title	Type of thrombotic event
End point description: Arterial events	
End point type	Secondary
End point timeframe: 3 years	

End point values	Rivaroxaban	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	95		
Units: percent				
number (not applicable)	10.5	3.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Type of thrombotic event

End point title	Type of thrombotic event
End point description:	
Venous events	
End point type	Secondary
End point timeframe:	
3 years	

End point values	Rivaroxaban	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	95		
Units: percent				
number (not applicable)	2.1	3.2		

Statistical analyses

Statistical analysis title	Venous events
Comparison groups	Rivaroxaban v Control
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.67
Method	Regression, Cox
Parameter estimate	Risk ratio (RR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	3.9

Secondary: Major bleeding

End point title	Major bleeding
End point description:	
End point type	Secondary
End point timeframe:	
3 years	

End point values	Rivaroxaban	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	95		
Units: Percent				
number (not applicable)	6.3	7.4		

Statistical analyses

Statistical analysis title	Major bleeding
Comparison groups	Rivaroxaban v Control
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.77
Method	Regression, Cox
Parameter estimate	Risk ratio (RR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2.46

Secondary: Nonmajor bleedings

End point title	Nonmajor bleedings
End point description:	
End point type	Secondary
End point timeframe:	
3 years	

End point values	Rivaroxaban	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	95		
Units: percent				
number (not applicable)	9.5	5.3		

Statistical analyses

Statistical analysis title	Non major bleeding
Comparison groups	Control v Rivaroxaban
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.28
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	5.17

Adverse events

Adverse events information

Timeframe for reporting adverse events:

3 years

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12

Reporting groups

Reporting group title	Total adverse events

Reporting group description: -

Serious adverse events	Total adverse events		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 190 (8.42%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	8		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant conditions			
subjects affected / exposed	4 / 190 (2.11%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 4		
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Endocarditis			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Systemic lupus erythematosus flare			
subjects affected / exposed	3 / 190 (1.58%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pulmonary hypertension			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pulmonary haemorrhage	Additional description: Pulmonary Haemorrhage due to capillaritis		
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Septic shock			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cholecystitis			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Soft tissue infection			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Total adverse events		
Total subjects affected by non-serious adverse events subjects affected / exposed	99 / 190 (52.11%)		
Cardiac disorders Hypertension subjects affected / exposed occurrences (all)	4 / 190 (2.11%) 4		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	13 / 190 (6.84%) 13		
Dizziness subjects affected / exposed occurrences (all)	9 / 190 (4.74%) 9		
Sciatica subjects affected / exposed occurrences (all)	3 / 190 (1.58%) 3		
Depression subjects affected / exposed occurrences (all)	5 / 190 (2.63%) 5		
Immune system disorders Systemic lupus erythematosus rash subjects affected / exposed occurrences (all)	7 / 190 (3.68%) 7		
Gastrointestinal disorders Gastroenteritis subjects affected / exposed occurrences (all)	10 / 190 (5.26%) 10		
Respiratory, thoracic and mediastinal disorders Chest pain subjects affected / exposed occurrences (all)	3 / 190 (1.58%) 3		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	16 / 190 (8.42%) 16		
Pneumonia			

subjects affected / exposed occurrences (all)	3 / 190 (1.58%) 3		
Renal and urinary disorders Urinary tract infection subjects affected / exposed occurrences (all)	 7 / 190 (3.68%) 7		
Infections and infestations Herpes virus infection subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all)	 1 / 190 (0.53%) 1 5 / 190 (2.63%) 5		
Metabolism and nutrition disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	 13 / 190 (6.84%) 13		

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.

Anticoagulation intensity was not measured, the study was underpowered to detect differences in patient subgroups, and the exploratory nature of post hoc analyses did not allow conclusions to be drawn

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31610549