



## 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 |
| Scientific contact           | Josefina Cortés, VHIR, fina.cortes@vhir.org                                |

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         |
| <b>Arm title</b>             | 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 m<sup>2</sup>)

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  $\geq 50$  mL/min.

|                                        |                   |
|----------------------------------------|-------------------|
| <b>Arm title</b>                       | 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).

| <b>Number of subjects in period 1</b> | 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

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### 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                |                    |

| <b>End point values</b>     | Rivaroxaban     | Control         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 95              | 95              |  |  |
| Units: units                | 11              | 6               |  |  |

### Statistical analyses

|                                         |                          |
|-----------------------------------------|--------------------------|
| <b>Statistical analysis title</b>       | 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                |                          |

| <b>End point values</b>     | 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                |                |

| <b>End point values</b>     | 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

| <b>Statistical analysis title</b>       | 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                |                    |

| <b>End point values</b>     | 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

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | 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<br>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<br>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<br>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<br>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                                                             |  |  |
|                                                              |                                                 |                                                                   |  |  |

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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 |
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Notes:

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### Online references

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