



## Clinical trial results:

### HEPARINA DE BAJO PESO MOLECULAR (HBPM) para la prevención de complicaciones derivadas de la insuficiencia placentaria en las pacientes de riesgo sin trombofilia: ensayo clínico multicéntrico randomizado

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2010-023597-39   |
| Trial protocol           | ES               |
| Global end of trial date | 21 December 2016 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 14 October 2021 |
| First version publication date | 14 October 2021 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | HOPPE-Trial |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |   |
|------------------------------------|---|
| ISRCTN number                      | - |
| ClinicalTrials.gov id (NCT number) | - |
| 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           | Academic Research Organization, VHIR, aro@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:

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**Results analysis stage**

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 21 December 2016 |
| Is this the analysis of the primary completion data? | No               |

|                                  |                  |
|----------------------------------|------------------|
| Global end of trial reached?     | Yes              |
| Global end of trial date         | 21 December 2016 |
| Was the trial ended prematurely? | No               |

Notes:

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**General information about the trial**

Main objective of the trial:

To evaluate the efficacy of treating patients in risk of maternofetal complications

Protection of trial subjects:

Blood analytics were done on 1st, 2nd and 3rd trimester of gestation. In the HBPM group, an additional analytics was done one week after starting treatment. Ecographies were done at 20 and 30-34 weeks of gestation

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 01 March 2012 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Spain: 278 |
| Worldwide total number of subjects   | 278        |
| EEA total number of subjects         | 278        |

Notes:

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**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)                      | 278 |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

|                              |     |
|------------------------------|-----|
| Number of subjects started   | 278 |
| Number of subjects completed | 278 |

### Period 1

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

Blinding implementation details:

The proposal intervention (subcutaneous administration) did not make possible to blind the study

### Arms

|                              |                     |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes                 |
| <b>Arm title</b>             | LMWH administration |

Arm description:

Low Molecular Weight Heparin administration

|  |                            |
|--|----------------------------|
| Arm type                               | Experimental               |
| Investigational medicinal product name | Heparin                    |
| Investigational medicinal product code |                            |
| Other name                             | Sodium Enoxaparin, Clexane |
| Pharmaceutical forms                   | Solution for injection     |
| Routes of administration               | Subcutaneous use           |

Dosage and administration details:

Daily dose of 40 mg (patients under 80Kg) or 60 mg (patients over 80Kg body weight at inclusion time).  
Dose was adjusted over the period, if necessary

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Control no treatment |
|------------------|----------------------|

Arm description: -

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

| Number of subjects in period 1 | LMWH administration | Control no treatment |
|--------------------------------|---------------------|----------------------|
| Started                        | 144                 | 134                  |
| Completed                      | 108                 | 116                  |
| Not completed                  | 36                  | 18                   |
| Lost to follow-up              | 31                  | 18                   |
| Protocol deviation             | 5                   | -                    |



## 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     | 278           | 278   |  |
| Age categorical        |               |       |  |
| Units: Subjects        |               |       |  |
| Adults (18-64 years)   | 278           | 278   |  |
| Gender categorical     |               |       |  |
| Units: Subjects        |               |       |  |
| Female                 | 278           | 278   |  |
| Male                   | 0             | 0     |  |

## End points

### End points reporting groups

|   |                      |
|---|----------------------|
| Reporting group title   | LMWH administration  |
| Reporting group description:<br>Low Molecular Weight Heparin administration |                      |
| Reporting group title   | Control no treatment |
| Reporting group description: -  |                      |

### Primary: Incidence of gestational complications

|   |  |
|---|--|
| End point title                           | Incidence of gestational complications |
| End point description:                    |  |
| End point type                            | Primary                                |
| End point timeframe:<br>End of gestations |  |

| End point values            | LMWH administration | Control no treatment |  |  |
|-----------------------------|---------------------|----------------------|--|--|
| Subject group type          | Reporting group     | Reporting group      |  |  |
| Number of subjects analysed | 144                 | 134                  |  |  |
| Units: percent              |                     |                      |  |  |
| number (not applicable)     | 32.0                | 34.7                 |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Overall complications                      |
| Comparison groups                       | LMWH administration v Control no treatment |
| Number of subjects included in analysis | 278  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | non-inferiority                            |
| P-value                                 | = 0.64                                     |
| Method                                  | t-test, 2-sided                            |
| Parameter estimate                      | Odds ratio (OR)                            |
| Point estimate                          | 1.13                                       |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 0.68                                       |
| upper limit                             | 1.85                                       |

**Secondary: Preeclampsia incidence**

|                 |                        |
|-----------------|------------------------|
| End point title | Preeclampsia incidence |
|-----------------|------------------------|

End point description:

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

End point timeframe:

All the study

| End point values            | LMWH administration | Control no treatment |  |  |
|-----------------------------|---------------------|----------------------|--|--|
| Subject group type          | Reporting group     | Reporting group      |  |  |
| Number of subjects analysed | 144                 | 134                  |  |  |
| Units: percent              |                     |                      |  |  |
| number (not applicable)     | 7.64                | 9.70                 |  |  |

**Statistical analyses**

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

|                   |  |
|-------------------|--|
| Comparison groups | LMWH administration v Control no treatment |
|-------------------|--|

|   |     |
|---|-----|
| Number of subjects included in analysis | 278 |
|---|-----|

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

|               |                 |
|---------------|-----------------|
| Analysis type | non-inferiority |
|---------------|-----------------|

|         |        |
|---------|--------|
| P-value | = 0.54 |
|---------|--------|

|        |                 |
|--------|-----------------|
| Method | t-test, 2-sided |
|--------|-----------------|

|                    |                 |
|--------------------|-----------------|
| Parameter estimate | Odds ratio (OR) |
|--------------------|-----------------|

|                |      |
|----------------|------|
| Point estimate | 0.77 |
|----------------|------|

Confidence interval

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

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

|             |      |
|-------------|------|
| lower limit | 0.33 |
|-------------|------|

|             |      |
|-------------|------|
| upper limit | 1.78 |
|-------------|------|

**Secondary: RCIU incidence**

|                 |                |
|-----------------|----------------|
| End point title | RCIU incidence |
|-----------------|----------------|

End point description:

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

End point timeframe:

All the study

| End point values            | LMWH administration | Control no treatment |  |  |
|-----------------------------|---------------------|----------------------|--|--|
| Subject group type          | Reporting group     | Reporting group      |  |  |
| Number of subjects analysed | 144                 | 134                  |  |  |
| Units: percent              |                     |                      |  |  |
| number (not applicable)     | 12.5                | 11.2                 |  |  |

### Statistical analyses

| Statistical analysis title              | RCIU incidence                             |
|---|--|
| Comparison groups                       | LMWH administration v Control no treatment |
| Number of subjects included in analysis | 278  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | non-inferiority                            |
| P-value                                 | = 0.736                                    |
| Method                                  | t-test, 2-sided                            |
| Parameter estimate                      | Odds ratio (OR)                            |
| Point estimate                          | 1.13                                       |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 0.55                                       |
| upper limit                             | 2.35                                       |

### Secondary: Small foetus

|                        |              |
|------------------------|--------------|
| End point title        | Small foetus |
| End point description: |              |
| End point type         | Secondary    |
| End point timeframe:   |              |
| All the study          |              |

| End point values            | LMWH administration | Control no treatment |  |  |
|-----------------------------|---------------------|----------------------|--|--|
| Subject group type          | Reporting group     | Reporting group      |  |  |
| Number of subjects analysed | 144                 | 134                  |  |  |
| Units: percent              |                     |                      |  |  |
| number (not applicable)     | 10.42               | 11.19                |  |  |

### Statistical analyses



|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Small foetus                               |
| Comparison groups                       | LMWH administration v Control no treatment |
| Number of subjects included in analysis | 278  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | non-inferiority                            |
| P-value                                 | = 0.834                                    |
| Method                                  | t-test, 2-sided                            |
| Parameter estimate                      | Odds ratio (OR)                            |
| Point estimate                          | 0.92                                       |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 0.43                                       |
| upper limit                             | 1.97                                       |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

End of study

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 14.1 |
|--------------------|------|

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Total adverse events |
|-----------------------|----------------------|

Reporting group description: -

| <b>Serious adverse events</b>                        | Total adverse events |  |  |
|--|----------------------|--|--|
| Total subjects affected by serious adverse events    |                      |  |  |
| subjects affected / exposed                          | 8 / 278 (2.88%)      |  |  |
| number of deaths (all causes)                        | 0                    |  |  |
| number of deaths resulting from adverse events       | 0                    |  |  |
| Nervous system disorders                             |                      |  |  |
| Intracranial venous thromboembolism                  |                      |  |  |
| subjects affected / exposed                          | 1 / 278 (0.36%)      |  |  |
| occurrences causally related to treatment / all      | 0 / 1                |  |  |
| deaths causally related to treatment / all           | 0 / 0                |  |  |
| Blood and lymphatic system disorders                 |                      |  |  |
| HELLP syndrome                                       |                      |  |  |
| subjects affected / exposed                          | 3 / 278 (1.08%)      |  |  |
| occurrences causally related to treatment / all      | 0 / 3                |  |  |
| deaths causally related to treatment / all           | 0 / 0                |  |  |
| Thromboembolism                                      |                      |  |  |
| subjects affected / exposed                          | 1 / 278 (0.36%)      |  |  |
| occurrences causally related to treatment / all      | 0 / 1                |  |  |
| deaths causally related to treatment / all           | 0 / 0                |  |  |
| General disorders and administration site conditions |                      |  |  |
| UCI ingress  |                      |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 278 (0.36%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Pulmonary oedema                                |                 |  |  |
| subjects affected / exposed                     | 2 / 278 (0.72%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

|   |                      |  |  |
|---|----------------------|--|--|
| <b>Non-serious adverse events</b>                     | Total adverse events |  |  |
| Total subjects affected by non-serious adverse events |                      |  |  |
| subjects affected / exposed                           | 2 / 278 (0.72%)      |  |  |
| Blood and lymphatic system disorders                  |                      |  |  |
| Epistaxis   |                      |  |  |
| subjects affected / exposed                           | 1 / 278 (0.36%)      |  |  |
| occurrences (all)                                     | 1                    |  |  |
| Platelet count decreased                              |                      |  |  |
| subjects affected / exposed                           | 1 / 278 (0.36%)      |  |  |
| occurrences (all)                                     | 1                    |  |  |

## 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.

|  |
|--|
| Double blinding was not possible due to nature of intervention. A 19% loss of adherence could make some results. A follow-up of mothers and infants is necessary to evaluate long-term effects of treatment on their health. |
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Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33472201>