



## Clinical trial results:

### An Open-label, Multi-centre Post-marketing Study to Assess the Efficacy and Safety of Voncento® in Subjects with Von Willebrand Disease

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2013-003305-25    |
| Trial protocol           | GB DE AT IE PL GR |
| Global end of trial date | 15 February 2018  |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 29 August 2018 |
| First version publication date | 29 August 2018 |

#### Trial information

##### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | CSLCT-BIO-12-83 |
|-----------------------|-----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02552576 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | CSL Behring GmbH  |
| Sponsor organisation address | Emil-von-Behring-Str.76, Marburg, Germany, 35041                            |
| Public contact               | Clinical Study Manager, CSL Behring GmbH ,<br>clinicaltrials@cslbehring.com |
| Scientific contact           | Clinical Study Manager, CSL Behring GmbH ,<br>clinicaltrials@cslbehring.com |

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? | Yes |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 07 March 2018    |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 15 February 2018 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to collect long-term data on the haemostatic efficacy of Voncento in subjects with VWD who require a VWF product to control an NSB event or as prophylaxis therapy.

Protection of trial subjects:

This study was carried out in accordance with the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) principles of Good Clinical Practice, the Declaration of Helsinki, and with standard operating procedures for clinical research and development at CSL Behring and at the Contract Research Organization involved. The design of the study was discussed and agreed with the Pharmacovigilance Risk Assessment Committee (PRAC), the CHMP, and the Blood Products Working Party (BPWP). The study was planned to comply with the requirements of the EMA CHMP Guideline on the Clinical Investigation of Human Plasma Derived VWF Products (CPMP/BPWG/220/02), specifically in relation to the directives regarding post-marketing studies.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 05 October 2015 |
| 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 | Poland: 11         |
| Country: Number of subjects enrolled | United Kingdom: 10 |
| Country: Number of subjects enrolled | Germany: 4         |
| Country: Number of subjects enrolled | Greece: 1          |
| Worldwide total number of subjects   | 26                 |
| EEA total number of subjects         | 26                 |

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          | 0 |

|                           |    |
|---------------------------|----|
| months)                   |    |
| Children (2-11 years)     | 4  |
| Adolescents (12-17 years) | 0  |
| Adults (18-64 years)      | 20 |
| From 65 to 84 years       | 2  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study was conducted at 10 to 15 sites in the United Kingdom, Germany, Greece, and Poland

### Period 1

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

### Arms

|                              |                      |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes                  |
| <b>Arm title</b>             | Voncento (on-demand) |

Arm description: -

|  |   |
|--|---|
| Arm type                               | Experimental                                  |
| Investigational medicinal product name | Voncento                                      |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Powder and solvent for solution for injection |
| Routes of administration               | Intravenous use                               |

Dosage and administration details:

Voncento was administered as bolus IV infusion with a rate not to exceed 6 mL/min. For on-demand treatment, for both adult and paediatric subjects, usually 40 to 80 IU/kg of Voncento corresponding to 20 to 40 IU FVIII:C/kg of body weight were recommended to achieve haemostasis. An initial dose of 80 IU/kg Voncento was to be required, especially in patients with Type 3 VWD.

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Voncento (prophylaxis) |
|------------------|------------------------|

Arm description: -

|  |   |
|--|---|
| Arm type                               | Experimental                                  |
| Investigational medicinal product name | Voncento                                      |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Powder and solvent for solution for injection |
| Routes of administration               | Intravenous use                               |

Dosage and administration details:

Voncento was administered as bolus IV infusion with a rate not to exceed 6 mL/min. For long-term prophylaxis in subjects 12 years and older, 25 to 40 IU of Voncento per kg body weight was to be considered at a frequency of 1 to 3 times per week; in subjects under 12 years, a prophylactic dose range of 40 to 80 IU Voncento/kg body weight was administered 1 to 3 times a week.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Voncento (on-demand) | Voncento (prophylaxis) |
|---|----------------------|------------------------|
| Started   | 11                   | 14                     |
| Completed   | 11                   | 10                     |
| Not completed                                       | 0                    | 4                      |
| Consent withdrawn by subject                        | -                    | 2                      |
| Pregnancy   | -                    | 1                      |
| Lost to follow-up                                   | -                    | 1                      |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Analysis was done on the Safety Population which comprised all subjects who received at least 1 dose of Voncento. Twenty-six (26) subjects were enrolled in the study, but 1 subject that did not meet inclusion criteria was enrolled by mistake and was terminated by the sponsor before receiving any study drug, therefore n=25.

## Baseline characteristics

### Reporting groups

Reporting group title

Overall Trial

Reporting group description: -

| Reporting group values                                | Overall Trial | Total |  |
|---|---------------|-------|--|
| Number of subjects                                    | 25            | 25    |  |
| Age categorical                                       |               |       |  |
| Units: Subjects                                       |               |       |  |
| In utero  | 0             | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0             | 0     |  |
| Newborns (0-27 days)                                  | 0             | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0             | 0     |  |
| Children (2-11 years)                                 | 4             | 4     |  |
| Adolescents (12-17 years)                             | 0             | 0     |  |
| Adults (18-64 years)                                  | 19            | 19    |  |
| From 65-84 years                                      | 2             | 2     |  |
| 85 years and over                                     | 0             | 0     |  |
| Age continuous  |               |       |  |
| Units: years  |               |       |  |
| arithmetic mean                                       | 35.8          |       |  |
| standard deviation                                    | ± 19.13       | -     |  |
| Gender categorical                                    |               |       |  |
| Units: Subjects                                       |               |       |  |
| Female  | 12            | 12    |  |
| Male  | 13            | 13    |  |

## End points

### End points reporting groups

|  |                          |
|--|--------------------------|
| Reporting group title  | Voncento (on-demand)     |
| Reporting group description: -   |                          |
| Reporting group title  | Voncento (prophylaxis)   |
| Reporting group description: -   |                          |
| Subject analysis set title   | Safety Population (SP)   |
| Subject analysis set type  | Safety analysis          |
| Subject analysis set description:<br>The Safety population comprised all subjects who received at least 1 dose of Voncento.  |                          |
| Subject analysis set title   | Efficacy Population (EP) |
| Subject analysis set type  | Sub-group analysis       |
| Subject analysis set description:<br>Efficacy population: The Efficacy population included all subjects of the safety population who had at least 1 post-baseline haemostatic efficacy assessment ("excellent", "good", "moderate", or "none") of Voncento for a non-surgical bleeding (NSB) event or a surgical procedure, or had at least 1 post-baseline assessment ("excellent", "good", "moderate", or "none") for a prophylaxis treatment. |                          |

### Primary: Investigator's Assessment of Haemostatic Efficacy on Non Surgical Bleeding (NSB) Events (EP)

|   |   |
|---|---|
| End point title   | Investigator's Assessment of Haemostatic Efficacy on Non Surgical Bleeding (NSB) Events (EP) <sup>[1]</sup> |
| End point description:<br>Efficacy Grading Scale:<br>Excellent = Haemostasis achieved / cessation of bleeding.<br>Good = Slight oozing / partial but adequate control of bleeding; did not require additional product for unplanned treatment.<br>Moderate = Moderate bleeding / moderate control of bleeding; required additional product for unplanned treatment.<br>None = Severe uncontrolled bleeding. |   |
| End point type  | Primary   |
| End point timeframe:<br>Up to 12 months   |   |
| Notes:<br>[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.<br>Justification: Only descriptive statistics were used   |   |

| End point values            | Voncento (on-demand) | Voncento (prophylaxis) |  |  |
|-----------------------------|----------------------|------------------------|--|--|
| Subject group type          | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed | 11                   | 14                     |  |  |
| Units: Number of NSB events |                      |                        |  |  |
| number (not applicable)     |                      |                        |  |  |
| Excellent                   | 22                   | 59                     |  |  |
| Good                        | 36                   | 5                      |  |  |
| Moderate                    | 11                   | 8                      |  |  |
| None                        | 0                    | 0                      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Subjects' Assessment of Haemostatic Efficacy per Bleeding Day on NSB events (EP)

|                 |   |
|-----------------|---|
| End point title | Subjects' Assessment of Haemostatic Efficacy per Bleeding Day on NSB events (EP) <sup>[2]</sup> |
|-----------------|---|

End point description:

Efficacy Grading Scale:

Excellent = Haemostasis achieved / cessation of bleeding.

Good = Slight oozing / partial but adequate control of bleeding; did not require additional product for unplanned treatment.

Moderate = Moderate bleeding / moderate control of bleeding; required additional product for unplanned treatment.

None = Severe uncontrolled bleeding.

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

End point timeframe:

Up to 12 months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were used

| End point values            | Voncento (on-demand) | Voncento (prophylaxis) |  |  |
|-----------------------------|----------------------|------------------------|--|--|
| Subject group type          | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed | 11                   | 14                     |  |  |
| Units: Number of NSB events |                      |                        |  |  |
| number (not applicable)     |                      |                        |  |  |
| Excellent                   | 14                   | 52                     |  |  |
| Good                        | 77                   | 45                     |  |  |
| Moderate                    | 49                   | 14                     |  |  |
| None                        | 0                    | 106                    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of NSB events per 3-month interval (EP)

|                 |   |
|-----------------|---|
| End point title | Number of NSB events per 3-month interval (EP) <sup>[3]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 12 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were used



| End point values            | Voncento (on-demand) | Voncento (prophylaxis) |  |  |
|-----------------------------|----------------------|------------------------|--|--|
| Subject group type          | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed | 11                   | 14                     |  |  |
| Units: Number of NSB events |                      |                        |  |  |
| number (not applicable)     |                      |                        |  |  |
| Month 1-3                   | 17                   | 21                     |  |  |
| Month 4-6                   | 13                   | 19                     |  |  |
| Month 7-9                   | 18                   | 28                     |  |  |
| Month 10-12                 | 34                   | 10                     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Total Annual Bleeding Rate for Treated NSB Events(EP)

|                 |  |
|-----------------|--|
| End point title | Total Annual Bleeding Rate for Treated NSB Events(EP) <sup>[4]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 12 months

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were used

| End point values                     | Voncento (on-demand) | Voncento (prophylaxis) |  |  |
|--------------------------------------|----------------------|------------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed          | 11                   | 14                     |  |  |
| Units: bleeds per year per subject   |                      |                        |  |  |
| arithmetic mean (standard deviation) | 6.2 (± 7.65)         | 6.2 (± 6.80)           |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of infusions per NSB event (EP)

|                 |   |
|-----------------|---|
| End point title | Number of infusions per NSB event (EP) <sup>[5]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 12 months

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were used

| End point values                     | Voncento (on-demand) | Voncento (prophylaxis) |  |  |
|--------------------------------------|----------------------|------------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed          | 11                   | 14                     |  |  |
| Units: infusions per event           |                      |                        |  |  |
| arithmetic mean (standard deviation) | 2.4 (± 2.85)         | 2.5 (± 4.37)           |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Total dose of Voncento per NSB event (EP)

|                 |  |
|-----------------|--|
| End point title | Total dose of Voncento per NSB event (EP) <sup>[6]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 12 months

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were used

| End point values                     | Voncento (on-demand) | Voncento (prophylaxis) |  |  |
|--------------------------------------|----------------------|------------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed          | 11                   | 14                     |  |  |
| Units: IU VWF:RCo/kg                 |                      |                        |  |  |
| arithmetic mean (standard deviation) | 147.6 (± 171.83)     | 167.2 (± 161.98)       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Investigator's Assessment of Hemostatic Efficacy on Prophylaxis Treatment (EP)

|                 |   |
|-----------------|---|
| End point title | Investigator's Assessment of Hemostatic Efficacy on Prophylaxis Treatment (EP) <sup>[7]</sup> |
|-----------------|---|

End point description:

Efficacy Grading Scale:

Excellent = Haemostasis achieved / cessation of bleeding.

Good = Slight oozing / partial but adequate control of bleeding; did not require additional product for unplanned treatment.

Moderate = Moderate bleeding / moderate control of bleeding; required additional product for unplanned

treatment.

None = Severe uncontrolled bleeding.

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

End point timeframe:

Up to 12 months

Notes:

[7] - 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: Data only collected on the Prophylaxis arm not the On-demand arm

| End point values            | Voncento<br>(prophylaxis) |  |  |  |
|-----------------------------|---------------------------|--|--|--|
| Subject group type          | Reporting group           |  |  |  |
| Number of subjects analysed | 14                        |  |  |  |
| Units: Number of events     |                           |  |  |  |
| number (not applicable)     |                           |  |  |  |
| Excellent                   | 12                        |  |  |  |
| Good                        | 2                         |  |  |  |
| Moderate                    | 1                         |  |  |  |
| None                        | 0                         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Subject's Assessment of Hemostatic Efficacy on Prophylaxis Treatment (EP)

|                 |  |
|-----------------|--|
| End point title | Subject's Assessment of Hemostatic Efficacy on Prophylaxis Treatment (EP) <sup>[8]</sup> |
|-----------------|--|

End point description:

Efficacy Grading Scale:

Excellent = Haemostasis achieved / cessation of bleeding.

Good = Slight oozing / partial but adequate control of bleeding; did not require additional product for unplanned treatment.

Moderate = Moderate bleeding / moderate control of bleeding; required additional product for unplanned treatment.

None = Severe uncontrolled bleeding.

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

End point timeframe:

Up to 12 months

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data only collected on the Prophylaxis arm not the On-demand arm

| End point values            | Voncento<br>(prophylaxis) |  |  |  |
|-----------------------------|---------------------------|--|--|--|
| Subject group type          | Reporting group           |  |  |  |
| Number of subjects analysed | 14                        |  |  |  |
| Units: Number of events     |                           |  |  |  |
| number (not applicable)     |                           |  |  |  |
| Excellent                   | 11                        |  |  |  |
| Good                        | 4                         |  |  |  |

|          |   |  |  |  |
|----------|---|--|--|--|
| Moderate | 1 |  |  |  |
| None     | 2 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Investigator's Assessment of Hemostatic Efficacy for Surgery (EP)

|                 |   |
|-----------------|---|
| End point title | Investigator's Assessment of Hemostatic Efficacy for Surgery (EP) |
|-----------------|---|

End point description:

Efficacy Grading Scale:

Excellent = Haemostasis achieved / cessation of bleeding.

Good = Slight oozing / partial but adequate control of bleeding; did not require additional product for unplanned treatment.

Moderate = Moderate bleeding / moderate control of bleeding; required additional product for unplanned treatment.

None = Severe uncontrolled bleeding.

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

End point timeframe:

Up to 12 months

| End point values                 | Voncento (on-demand) | Voncento (prophylaxis) |  |  |
|----------------------------------|----------------------|------------------------|--|--|
| Subject group type               | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed      | 11                   | 14                     |  |  |
| Units: Number of surgical events |                      |                        |  |  |
| number (not applicable)          |                      |                        |  |  |
| Excellent                        | 4                    | 3                      |  |  |
| Good                             | 5                    | 0                      |  |  |
| Moderate                         | 0                    | 0                      |  |  |
| None                             | 0                    | 0                      |  |  |
| Missing                          | 0                    | 1                      |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Investigator's Assessment of Blood Loss for Surgery (EP)

|                 |  |
|-----------------|--|
| End point title | Investigator's Assessment of Blood Loss for Surgery (EP) |
|-----------------|--|

End point description:

The blood loss was judged to be "less", "equivalent", or "more" compared with the expected blood loss from a subject without a bleeding disorder undergoing the same procedure.

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

End point timeframe:

Up to 12 months

| End point values                 | Voncento (on-demand) | Voncento (prophylaxis) |  |  |
|----------------------------------|----------------------|------------------------|--|--|
| Subject group type               | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed      | 11                   | 14                     |  |  |
| Units: Number of surgical events |                      |                        |  |  |
| number (not applicable)          |                      |                        |  |  |
| Less                             | 1                    | 1                      |  |  |
| Equivalent                       | 8                    | 2                      |  |  |
| More                             | 0                    | 0                      |  |  |
| Missing                          | 0                    | 1                      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of infusions required to treat a surgical bleeding event (EP)

|                 |  |
|-----------------|--|
| End point title | Number of infusions required to treat a surgical bleeding event (EP) |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 12 months

| End point values                     | Voncento (on-demand) | Voncento (prophylaxis) |  |  |
|--------------------------------------|----------------------|------------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed          | 4                    | 4                      |  |  |
| Units: Number of infusions           |                      |                        |  |  |
| arithmetic mean (standard deviation) | 15.8 (± 9.6)         | 3.3 (± 2.63)           |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Dose per infusion of Voncento required to treat a surgical bleeding event (EP)

|                 |  |
|-----------------|--|
| End point title | Dose per infusion of Voncento required to treat a surgical bleeding event (EP) |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 12 months

| End point values                     | Voncento (on-demand) | Voncento (prophylaxis) |  |  |
|--------------------------------------|----------------------|------------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed          | 4                    | 4                      |  |  |
| Units: IU VWF:RCo/kg                 |                      |                        |  |  |
| arithmetic mean (standard deviation) | 58.48 (± 37.670)     | 104.53 (± 87.105)      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Summary of Inhibitors (SP)

|                 |                            |
|-----------------|----------------------------|
| End point title | Summary of Inhibitors (SP) |
|-----------------|----------------------------|

End point description:

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

End point timeframe:

Up to 12 months

| End point values            | Voncento (on-demand) | Voncento (prophylaxis) |  |  |
|-----------------------------|----------------------|------------------------|--|--|
| Subject group type          | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed | 11                   | 14                     |  |  |
| Units: BU/mL                |                      |                        |  |  |
| number (not applicable)     |                      |                        |  |  |
| von Willebrand Inhibitor    | 0                    | 0                      |  |  |
| Factor VIII Inhibitor       | 0                    | 0                      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with Treatment Emergent Adverse Events (TEAEs)

|                 |   |
|-----------------|---|
| End point title | Number of Subjects with Treatment Emergent Adverse Events (TEAEs) |
|-----------------|---|

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End point description:

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

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End point timeframe:

Up to 12 months

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| End point values            | Voncento (on-demand) | Voncento (prophylaxis) |  |  |
|-----------------------------|----------------------|------------------------|--|--|
| Subject group type          | Reporting group      | Reporting group        |  |  |
| Number of subjects analysed | 11                   | 14                     |  |  |
| Units: Number of subjects   |                      |                        |  |  |
| number (not applicable)     |                      |                        |  |  |
| TEAEs                       | 7                    | 12                     |  |  |
| Serious TEAEs               | 1                    | 1                      |  |  |
| TEAEs of special interest   | 0                    | 2                      |  |  |
| Treatment-related TEAEs     | 0                    | 1                      |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

12 months per subject

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Voncento (on-demand) |
|-----------------------|----------------------|

Reporting group description: -

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Voncento (prophylaxis) |
|-----------------------|------------------------|

Reporting group description: -

| Serious adverse events                            | Voncento (on-demand) | Voncento (prophylaxis) |  |
|---|----------------------|------------------------|--|
| Total subjects affected by serious adverse events |                      |                        |  |
| subjects affected / exposed                       | 1 / 11 (9.09%)       | 1 / 14 (7.14%)         |  |
| number of deaths (all causes)                     | 0                    | 0                      |  |
| number of deaths resulting from adverse events    | 0                    | 0                      |  |
| Gastrointestinal disorders                        |                      |                        |  |
| Abdominal pain                                    |                      |                        |  |
| subjects affected / exposed                       | 0 / 11 (0.00%)       | 1 / 14 (7.14%)         |  |
| occurrences causally related to treatment / all   | 0 / 0                | 0 / 1                  |  |
| deaths causally related to treatment / all        | 0 / 0                | 0 / 0                  |  |
| Respiratory, thoracic and mediastinal disorders   |                      |                        |  |
| Asthma  |                      |                        |  |
| subjects affected / exposed                       | 1 / 11 (9.09%)       | 0 / 14 (0.00%)         |  |
| occurrences causally related to treatment / all   | 0 / 2                | 0 / 0                  |  |
| deaths causally related to treatment / all        | 0 / 0                | 0 / 0                  |  |

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

| Non-serious adverse events                            | Voncento (on-demand) | Voncento (prophylaxis) |  |
|---|----------------------|------------------------|--|
| Total subjects affected by non-serious adverse events |                      |                        |  |
| subjects affected / exposed                           | 7 / 11 (63.64%)      | 12 / 14 (85.71%)       |  |



|   |   |   |  |
|---|---|---|--|
| Vascular disorders<br>Haematoma<br>subjects affected / exposed<br>occurrences (all)   | 0 / 11 (0.00%)<br>0   | 1 / 14 (7.14%)<br>1   |  |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)<br><br>Injection site pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Pyrexia<br>subjects affected / exposed<br>occurrences (all) | 0 / 11 (0.00%)<br>0<br><br>0 / 11 (0.00%)<br>0<br><br>0 / 11 (0.00%)<br>0 | 1 / 14 (7.14%)<br>1<br><br>1 / 14 (7.14%)<br>6<br><br>1 / 14 (7.14%)<br>1 |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)  | 1 / 11 (9.09%)<br>1   | 1 / 14 (7.14%)<br>1   |  |
| Psychiatric disorders<br>Compulsive lip biting<br>subjects affected / exposed<br>occurrences (all)<br><br>Depression<br>subjects affected / exposed<br>occurrences (all)<br><br>Sleep disorder<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 11 (0.00%)<br>0<br><br>0 / 11 (0.00%)<br>0<br><br>1 / 11 (9.09%)<br>1 | 1 / 14 (7.14%)<br>1<br><br>1 / 14 (7.14%)<br>1<br><br>0 / 14 (0.00%)<br>0 |  |
| Investigations<br>Blood iron decreased<br>subjects affected / exposed<br>occurrences (all)  | 0 / 11 (0.00%)<br>0   | 1 / 14 (7.14%)<br>1   |  |
| Injury, poisoning and procedural complications<br>Contusion<br>subjects affected / exposed<br>occurrences (all)   | 0 / 11 (0.00%)<br>0   | 1 / 14 (7.14%)<br>1   |  |

|   |  |   |  |
|---|--|---|--|
| Face injury<br>subjects affected / exposed<br>occurrences (all)   | 0 / 11 (0.00%)<br>0  | 1 / 14 (7.14%)<br>1   |  |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)   | 0 / 11 (0.00%)<br>0  | 1 / 14 (7.14%)<br>1   |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Seizure<br>subjects affected / exposed<br>occurrences (all)<br><br>Tongue biting<br>subjects affected / exposed<br>occurrences (all) | 0 / 11 (0.00%)<br>0<br><br>1 / 11 (9.09%)<br>1<br><br>0 / 11 (0.00%)<br>0<br><br>0 / 11 (0.00%)<br>0 | 2 / 14 (14.29%)<br>11<br><br>0 / 14 (0.00%)<br>0<br><br>1 / 14 (7.14%)<br>11<br><br>1 / 14 (7.14%)<br>1 |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Iron deficiency anaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Microcytosis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 11 (0.00%)<br>0<br><br>1 / 11 (9.09%)<br>1<br><br>1 / 11 (9.09%)<br>1                            | 1 / 14 (7.14%)<br>1<br><br>0 / 14 (0.00%)<br>0<br><br>0 / 14 (0.00%)<br>0                               |  |
| Eye disorders<br>Dry eye<br>subjects affected / exposed<br>occurrences (all)  | 0 / 11 (0.00%)<br>0  | 1 / 14 (7.14%)<br>1   |  |
| Gastrointestinal disorders<br>Diarrhoea   |  |   |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 11 (0.00%) | 2 / 14 (14.29%) |  |
| occurrences (all)                               | 0              | 2               |  |
| Nausea  |                |                 |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                               | 1              | 1               |  |
| Abdominal pain upper                            |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Constipation                                    |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Dry mouth                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Faeces discoloured                              |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Vomiting  |                |                 |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 14 (0.00%)  |  |
| occurrences (all)                               | 1              | 0               |  |
| Skin and subcutaneous tissue disorders          |                |                 |  |
| Dermatitis contact                              |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Swelling face                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Renal and urinary disorders                     |                |                 |  |
| Dysuria   |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Musculoskeletal and connective tissue disorders |                |                 |  |
| Arthralgia                                      |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 2 / 14 (14.29%) |  |
| occurrences (all)                               | 0              | 13              |  |
| Pain in extremity                               |                |                 |  |

|                                   |                |                 |  |
|-----------------------------------|----------------|-----------------|--|
| subjects affected / exposed       | 1 / 11 (9.09%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                 | 1              | 2               |  |
| Arthritis                         |                |                 |  |
| subjects affected / exposed       | 0 / 11 (0.00%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                 | 0              | 1               |  |
| Back pain                         |                |                 |  |
| subjects affected / exposed       | 0 / 11 (0.00%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                 | 0              | 1               |  |
| Osteitis                          |                |                 |  |
| subjects affected / exposed       | 0 / 11 (0.00%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                 | 0              | 1               |  |
| Infections and infestations       |                |                 |  |
| Nasopharyngitis                   |                |                 |  |
| subjects affected / exposed       | 1 / 11 (9.09%) | 2 / 14 (14.29%) |  |
| occurrences (all)                 | 1              | 7               |  |
| Acute sinusitis                   |                |                 |  |
| subjects affected / exposed       | 0 / 11 (0.00%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                 | 0              | 1               |  |
| Bronchitis                        |                |                 |  |
| subjects affected / exposed       | 0 / 11 (0.00%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                 | 0              | 1               |  |
| Ear infection                     |                |                 |  |
| subjects affected / exposed       | 0 / 11 (0.00%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                 | 0              | 1               |  |
| Gastroenteritis                   |                |                 |  |
| subjects affected / exposed       | 0 / 11 (0.00%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                 | 0              | 1               |  |
| Otitis media                      |                |                 |  |
| subjects affected / exposed       | 0 / 11 (0.00%) | 1 / 14 (7.14%)  |  |
| occurrences (all)                 | 0              | 1               |  |
| Post procedural infection         |                |                 |  |
| subjects affected / exposed       | 1 / 11 (9.09%) | 0 / 14 (0.00%)  |  |
| occurrences (all)                 | 1              | 0               |  |
| Upper respiratory tract infection |                |                 |  |
| subjects affected / exposed       | 1 / 11 (9.09%) | 0 / 14 (0.00%)  |  |
| occurrences (all)                 | 1              | 0               |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 11 (0.00%)<br>0 | 1 / 14 (7.14%)<br>1 |  |
| Metabolism and nutrition disorders<br>Iron deficiency<br>subjects affected / exposed<br>occurrences (all) | 0 / 11 (0.00%)<br>0 | 1 / 14 (7.14%)<br>1 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment   |
|----------------|---|
| 27 August 2015 | <ul style="list-style-type: none"><li>• Prophylaxis treatment was added as treatment option in the study</li><li>• The removal of the age restriction for participating subjects</li><li>• Overall study duration was expected to be 2.5 years instead of 4</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported