



## Clinical trial results:

### Clinical Study to Investigate the Long-Term Efficacy, Safety, and Immunogenicity of human-cl rhFVIII in Previously Treated Patients with Severe Haemophilia A – Extension Study to GENA-01

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2010-023242-69 |
| Trial protocol           | DE BG          |
| Global end of trial date | 30 August 2012 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 18 December 2016 |
| First version publication date | 18 December 2016 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | GENA-11 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01341912 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Octapharma AG  |
| Sponsor organisation address | Seidenstraße 2, Lachen, Switzerland, CH-8853                                     |
| Public contact               | Johann Bichler, Octapharma AG, +41 (0)554512177,<br>johann.bichler@octapharma.ch |
| Scientific contact           | Johann Bichler, Octapharma AG, +41 (0)554512177,<br>johann.bichler@octapharma.ch |

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**

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|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 16 July 2013 |
| Is this the analysis of the primary completion data? | No           |

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|                                  |                |
|----------------------------------|----------------|
| Global end of trial reached?     | Yes            |
| Global end of trial date         | 30 August 2012 |
| Was the trial ended prematurely? | Yes            |

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Notes:

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**General information about the trial**

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Main objective of the trial:

To determine the long-term immunogenicity and tolerability of human-cl rhFVIII in previously treated patients with severe haemophilia A.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and ICH-GCP, and national regulatory requirements. In- and exclusion criteria were carefully defined in order to protect subjects from contraindications, interactions with other medication and safety factors associated with the investigational medicinal product. Throughout the study safety was assessed, such as occurrence of adverse events, lab values, vital signs and physical examinations. In particular, patients were checked at pre-specified times whether they had developed an inhibitor to factor VIII.

Background therapy: -

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 14 May 2012 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | No          |

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Bulgaria: 3 |
| Worldwide total number of subjects   | 3           |
| EEA total number of subjects         | 3           |

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Notes:

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**Subjects enrolled per age group**

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|   |   |
|---|---|
| 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)                      | 2 |
| From 65 to 84 years                       | 1 |

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|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

Participation in this open phase 3b study was open to all patients who had completed the GENA-01 study with at least 50 exposure days (EDs) after at least 6 months of study participation.

### Pre-assignment

Screening details:

NA

### Period 1

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

Blinding implementation details:

NA

### Arms

|           |                  |
|-----------|------------------|
| Arm title | Human-cl rhFVIII |
|-----------|------------------|

Arm description:

Participation in this open phase 3b study was open to all patients who had completed the GENA-01 study with at least 50 exposure days (EDs) after at least 6 months of study participation. Overall, therefore, 21 patients would theoretically have been eligible for enrolment into GENA-11. Only 3 patients from Bulgaria participated in GENA-11 study.

|  |  |
|--|--|
| Arm type                               | Experimental                                       |
| Investigational medicinal product name | Human-cl rhFVIII                                   |
| Investigational medicinal product code |  |
| Other name                             | Nuwiq  |
| Pharmaceutical forms                   | Concentrate and solvent for solution for injection |
| Routes of administration               | Intravenous use                                    |

Dosage and administration details:

The dosing recommendations in GENA-11 were the same as in its predecessor study GENA-01:

- Minor haemorrhage (superficial muscle or soft tissue and oral bleeds): 20–30 IU FVIII/kg BW (body weight) every 12–24 hours until BE is resolved.
- Moderate to major haemorrhage (haemorrhage into muscles, into oral cavity; haemarthrosis; known trauma): 30–40 IU FVIII/kg BW. Repeat one dose every 12–24 hours until BE is resolved.
- Major to life-threatening BEs (intracranial, intra-abdominal, gastrointestinal or intrathoracic bleeds, central nervous system bleeds, bleeding in retropharyngeal spaces or iliopsoas sheath, eyes/retina, fractures or head trauma): initial dose of 50–60 IU FVIII/kg BW. Repeat dose of 20–25 IU FVIII/kg BW every 8–12 hours until BE is resolved.

|                                       |                  |
|---------------------------------------|------------------|
| <b>Number of subjects in period 1</b> | Human-cl rhFVIII |
| Started                               | 3                |
| Completed                             | 0                |
| Not completed                         | 3                |
| Consent withdrawn by subject          | 3                |



## Baseline characteristics

### Reporting groups

|                                |               |
|--------------------------------|---------------|
| Reporting group title          | Overall trial |
| Reporting group description: - |               |

| Reporting group values                             | Overall trial | Total |  |
|--|---------------|-------|--|
| Number of subjects                                 | 3             | 3     |  |
| Age categorical                                    |               |       |  |
| Units: Subjects                                    |               |       |  |
| In utero   | 0             | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) | 0             | 0     |  |
| Newborns (0-27 days)                               | 0             | 0     |  |
| Infants and toddlers (28 days-23 months)           | 0             | 0     |  |
| Children (2-11 years)                              | 0             | 0     |  |
| Adolescents (12-17 years)                          | 0             | 0     |  |
| Adults (18-64 years)                               | 2             | 2     |  |
| From 65-84 years                                   | 1             | 1     |  |
| 85 years and over                                  | 0             | 0     |  |
| Gender categorical                                 |               |       |  |
| Units: Subjects                                    |               |       |  |
| Female   | 0             | 0     |  |
| Male   | 3             | 3     |  |

### Subject analysis sets

|                            |                  |
|----------------------------|------------------|
| Subject analysis set title | BLEED population |
| Subject analysis set type  | Safety analysis  |

Subject analysis set description:

The study population for which data was summarised is the BLEED population, i.e., the population of patients with documented BEs for which any amount of treatment with Human-cl rhFVIII was documented. The BLEED population in this study is identical with the safety (SAF) population, i.e., the population of patients who received at least one dose of Human-cl rhFVIII and were evaluated for AEs.

| Reporting group values                             | BLEED population |  |  |
|--|------------------|--|--|
| Number of subjects                                 | 3                |  |  |
| Age categorical                                    |                  |  |  |
| Units: Subjects                                    |                  |  |  |
| In utero   | 0                |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 0                |  |  |
| Newborns (0-27 days)                               | 0                |  |  |
| Infants and toddlers (28 days-23 months)           | 0                |  |  |
| Children (2-11 years)                              | 0                |  |  |
| Adolescents (12-17 years)                          | 0                |  |  |
| Adults (18-64 years)                               | 2                |  |  |
| From 65-84 years                                   | 1                |  |  |
| 85 years and over                                  | 0                |  |  |

|                    |   |  |  |
|--------------------|---|--|--|
| Gender categorical |   |  |  |
| Units: Subjects    |   |  |  |
| Female             | 0 |  |  |
| Male               | 3 |  |  |

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## End points

### End points reporting groups

|  |                  |
|--|------------------|
| Reporting group title  | Human-cl rhFVIII |
| Reporting group description:   |                  |
| Participation in this open phase 3b study was open to all patients who had completed the GENA-01 study with at least 50 exposure days (EDs) after at least 6 months of study participation. Overall, therefore, 21 patients would theoretically have been eligible for enrolment into GENA-11. Only 3 patients from Bulgaria participated in GENA-11 study.  |                  |
| Subject analysis set title   | BLEED population |
| Subject analysis set type  | Safety analysis  |
| Subject analysis set description:  |                  |
| The study population for which data was summarised is the BLEED population, i.e., the population of patients with documented BEs for which any amount of treatment with Human-cl rhFVIII was documented. The BLEED population in this study is identical with the safety (SAF) population, i.e., the population of patients who received at least one dose of Human-cl rhFVIII and were evaluated for AEs. |                  |

### Primary: Long-term immunogenicity of Human-cl rhFVIII

|  |   |
|--|---|
| End point title  | Long-term immunogenicity of Human-cl rhFVIII <sup>[1]</sup> |
| End point description:   |   |
| The long-term immunogenicity of Human-cl rhFVIII was to be assessed by determining FVIII inhibitor activity at 3-monthly intervals until study completion by the modified Bethesda assay (Nijmegen modification) using congenital FVIII-deficient human plasma spiked with Human-cl rhFVIII as a test base; anti-rhFVIII antibodies were to be measured at the same time points. An inhibitor test was considered negative if the titer was <0.6 BU. |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| Measurement at 3-monthly intervals until study completion  |   |
| Notes:   |   |
| [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.  |   |
| Justification: The original Statistical Analysis Plan (SAP) prepared for this study was amended once in response to the study being terminated prematurely. Because most of the originally planned statistical analyses would not have been significant with only 3 enrolled patients, the results of this study are summarised descriptively only.  |   |

| End point values                   | Human-cl rhFVIII |  |  |  |
|------------------------------------|------------------|--|--|--|
| Subject group type                 | Reporting group  |  |  |  |
| Number of subjects analysed        | 3                |  |  |  |
| Units: Occurrence of Inhibitor     |                  |  |  |  |
| Occurrence of Inhibitor >0.6 BU/mL | 0                |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Long-term Tolerability of Human-cl rhFVIII

|  |   |
|--|---|
| End point title  | Long-term Tolerability of Human-cl rhFVIII <sup>[2]</sup> |
| End point description:   |   |
| Long-term clinical tolerability was assessed by monitoring AEs throughout the study. |   |
| End point type   | Primary   |



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End point timeframe:

throughout the study

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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: The original Statistical Analysis Plan (SAP) prepared for this study was amended once in response to the study being terminated prematurely. Because most of the originally planned statistical analyses would not have been significant with only 3 enrolled patients, the results of this study are summarised descriptively only.

| End point values            | BLEED<br>population  |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 3                    |  |  |  |
| Units: Occurrence of AEs    |                      |  |  |  |
| Occurrence of AEs           | 0                    |  |  |  |
| Occurrence of SAEs          | 0                    |  |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

AE were reported throughout the whole study. 24 hours SAE reporting requirement. Waiver from 24 hours SAE reporting: hospitalization for the treatment of a (disease-related) BE assessed as unrelated to IMP treatment.

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Adverse event reporting additional description:

All SAEs, whether suspected to be related to study treatment or not, are reported by telephone, fax or e-mail immediately to the responsible Clinical Project Manager, study monitor, or to the responsible local CRO. AEs were evaluated at each patient visit.

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

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### Dictionary used

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|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 15.0   |

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

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Notes:

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

Justification: No AEs or SAEs occurred in any of the 3 patients.

## **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**

None reported