



Clinical trial results:

Clinical Study in Previously Treated Children with Severe Haemophilia A to Investigate the Long-Term Immunogenicity, Tolerability and Efficacy of Human-cl rhFVIII

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2011-001785-17 |
| Trial protocol | GB FR CZ PL RO |
| Global end of trial date | 13 May 2016 |

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-13 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| 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, johann.bichler@octapharma.ch |
| Scientific contact | Johann Bichler, Octapharma AG, +41 (0)554512177, 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? | Yes |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 22 November 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 May 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary endpoints of this study were to assess the long-term immunogenicity and tolerability of Human-cl rhFVIII.

Long-term immunogenicity was assessed on the basis of inhibitor activity, determined using the modified Bethesda assay (Nijmegen modification) and anti-rhFVIII antibody measurements.

Long-term clinical tolerability was assessed by monitoring adverse events (AEs) throughout the study duration.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. It was submitted to an IEC and it was conducted in compliance with the protocol, GCP regulations and applicable regulatory requirements. Inclusion and exclusion criteria were carefully defined in order to protect subjects from contraindications, interactions with other medication and safety factors associated with the IMP.

Throughout the study safety was assessed such as occurrence of AEs, measuring vital signs and routine safety laboratory parameters at pre-defined time points. Also inhibitors against FVIII and anti-rhFVIII antibodies were determined at pre-determined time points.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 25 October 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Russian Federation: 9 |
| Country: Number of subjects enrolled | Poland: 24 |
| Country: Number of subjects enrolled | Romania: 3 |
| Country: Number of subjects enrolled | United Kingdom: 10 |
| Country: Number of subjects enrolled | Czech Republic: 1 |
| Country: Number of subjects enrolled | France: 2 |
| Worldwide total number of subjects | 49 |
| EEA total number of subjects | 40 |

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) | 43 |
| Adolescents (12-17 years) | 6 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participation in GENA-13 was open to all evaluable patients who had completed study GENA-03 with a study participation period of at least 6 months. The screening visit for GENA-13 coincided with the study completion visit of GENA-03.

Pre-assignment

Screening details:

Inclusion criteria:

Completion of study GENA-03 by having a study participation period of at least 6 months, provided that prophylaxis with Human-cl rhFVIII continued without intermediate interruption.
Voluntarily given, fully informed written and signed consent obtained from the parents (or legal guardians)

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:

Prophylactic and on-demand treatment with Human-cl rhFVIII

Participation in GENA-13 was open to all evaluable patients who had completed study GENA-03 with a study participation period of 6 months. The mean duration of prophylactic treatment in GENA-03 had been 6.6 ± 1.4 months (median: 6.3 months, range 1.3–9.8). The screening visit for GENA-13 coincided with the study completion visit of GENA-03.

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

Dosage and administration details:

The dosing recommendations in GENA-13 were the same as in its predecessor study GENA-03.

For prophylactic treatment, an every-other-day or a 3-times-a-week dosage regimen was available for selection. Regardless of the selected regimen, the prophylactic dose was 30–40 IU FVIII/kg BW. Two dose escalations of approximately +5 IU FVIII/kg BW each were recommended if two or more spontaneous BEs within one month were reported.

For the treatment of Bleeding Episodes (BE), the dosage and duration depended on the location and extent of bleeding as well as on the clinical situation of the patient.

| Number of subjects in period 1 | Human-cl rhFVIII |
|---------------------------------------|------------------|
| Started | 49 |
| Completed | 44 |
| Not completed | 5 |
| Adverse event, serious fatal | 1 |
| Consent withdrawn by subject | 3 |
| Protocol deviation | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall trial |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Overall trial | Total | |
|---------------------------------------|---------------|-------|--|
| Number of subjects | 49 | 49 | |
| Age categorical Units: Subjects | | | |
| Children (2-11 years) | 43 | 43 | |
| Adolescents (12-17 years) | 6 | 6 | |
| Gender categorical Units: Subjects | | | |
| Male | 49 | 49 | |
| Female | 0 | 0 | |

Subject analysis sets

| | |
|----------------------------|-------------------------|
| Subject analysis set title | Safety population (SAF) |
|----------------------------|-------------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

All subjects who received at least one dose of Human-cl rhFVIII

| Reporting group values | Safety population (SAF) | | |
|---------------------------------------|-------------------------|--|--|
| Number of subjects | 49 | | |
| Age categorical Units: Subjects | | | |
| Children (2-11 years) | 43 | | |
| Adolescents (12-17 years) | 6 | | |
| Gender categorical Units: Subjects | | | |
| Male | 49 | | |
| Female | | | |

End points

End points reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Human-cl rhFVIII |
|-----------------------|------------------|

Reporting group description:

Prophylactic and on-demand treatment with Human-cl rhFVIII

Participation in GENA-13 was open to all evaluable patients who had completed study GENA-03 with a study participation period of 6 months. The mean duration of prophylactic treatment in GENA-03 had been 6.6 ± 1.4 months (median: 6.3 months, range 1.3–9.8). The screening visit for GENA-13 coincided with the study completion visit of GENA-03.

| | |
|----------------------------|-------------------------|
| Subject analysis set title | Safety population (SAF) |
|----------------------------|-------------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

All subjects who received at least one dose of Human-cl rhFVIII

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

| | |
|-----------------|---|
| End point title | Long-term immunogenicity of Human-cl rhFVIII ^[1] |
|-----------------|---|

End point description:

Immunogenicity was to be assessed on the basis of FVIII inhibitors and anti-rhFVIII antibodies determined by central laboratories at predefined time points and whenever inhibitor development was suspected. An inhibitor test was considered to be negative if the titer was <0.6 BU.

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

End point timeframe:

throughout the study

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: Because this was an uncontrolled study, no inferential analysis involving formal testing and, consequently, no formal sample size estimation were performed. The statistical analysis of all endpoints was performed descriptively.

| End point values | Safety population (SAF) | | | |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 49 | | | |
| 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 ^[2] |
|-----------------|---|

End point description:

Monitoring of adverse events (AEs) and serious adverse events (SAEs), vital signs, laboratory parameters (haematology and clinical chemistry), and physical examinations (including the Haemophilia Joint Health Score, HJHS) throughout the study duration.

Temporally related AEs: within 24 hours after the end of infusion

AEs related to surgical procedures: AEs occurring between the start of surgical prophylaxis and the return to routine prophylaxis.

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

End point timeframe:

Throughout the study

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: Because this was an uncontrolled study, no inferential analysis involving formal testing and, consequently, no formal sample size estimation were performed. The statistical analysis of all endpoints was performed descriptively.

| | | | | |
|--------------------------------------|-------------------------|--|--|--|
| End point values | Safety population (SAF) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 49 | | | |
| Units: Occurrence of Adverse Events | | | | |
| Adverse events (AEs) | 317 | | | |
| Serious Adverse events (SAEs) | 30 | | | |
| Severe AEs | 8 | | | |
| Possibly/probably related AEs (ADRs) | 2 | | | |
| Temporally related AEs | 127 | | | |
| AEs related to surgical procedures | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for reporting AEs:

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.

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.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | Safety analysis population SAF |
|-----------------------|--------------------------------|

Reporting group description:

all patients exposed to treatment

| Serious adverse events | Safety analysis population SAF | | |
|---|--------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 49 (42.86%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Osteoma | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Head injury | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Haematoma | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Synoviorthesis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Application site erosion | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hernia | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device occlusion | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device damage | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|----------------------------------|--|--|
| Multi-organ failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 49 (2.04%) 0 / 1 0 / 1 | | |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 49 (2.04%) 0 / 1 0 / 0 | | |
| Abdominal pain subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 49 (2.04%) 0 / 1 0 / 0 | | |
| Skin and subcutaneous tissue disorders Ingrowing nail subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 49 (2.04%) 0 / 1 0 / 0 | | |
| Renal and urinary disorders Haematuria subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 49 (4.08%) 0 / 2 0 / 0 | | |
| Renal colic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 49 (2.04%) 0 / 1 0 / 0 | | |
| Musculoskeletal and connective tissue disorders Haemarthrosis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 49 (2.04%) 0 / 1 0 / 0 | | |
| Infections and infestations Device related infection | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 3 / 49 (6.12%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Catheter site infection | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| | | | |
|---|--------------------------------|--|--|
| Non-serious adverse events | Safety analysis population SAF | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 45 / 49 (91.84%) | | |
| Investigations | | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 3 / 49 (6.12%) | | |
| occurrences (all) | 4 | | |
| Injury, poisoning and procedural | | | |

| | | | |
|---|---|--|--|
| complications Head injury subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 6 / 49 (12.24%) 19 | | |
| General disorders and administration site conditions Chills subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) | 6 / 49 (12.24%) 10 6 / 49 (12.24%) 11 | | |
| Blood and lymphatic system disorders Haematuria subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 4 / 49 (8.16%) 4 3 / 49 (6.12%) 4 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 9 / 49 (18.37%) 11 | | |
| Musculoskeletal and connective tissue disorders Pain in extremity | | | |

| | | | |
|--|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 5 / 49 (10.20%) 6 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 10 / 49 (20.41%) | | |
| occurrences (all) | 15 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 17 / 49 (34.69%) | | |
| occurrences (all) | 28 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 7 / 49 (14.29%) | | |
| occurrences (all) | 11 | | |
| Rhinitis | | | |
| subjects affected / exposed | 8 / 49 (16.33%) | | |
| occurrences (all) | 14 | | |
| Tooth abscess | | | |
| subjects affected / exposed | 4 / 49 (8.16%) | | |
| occurrences (all) | 4 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 9 / 49 (18.37%) | | |
| occurrences (all) | 17 | | |
| Varicella | | | |
| subjects affected / exposed | 5 / 49 (10.20%) | | |
| occurrences (all) | 5 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 19 August 2011 | Amendment 1: only applied to UK Limitation of the individual study duration for each participating patient to 2 years +/- 1 month. |
| 21 August 2013 | Amendment 2: The planned clinical end of the study was moved from Q1 2014 to 15-Sep-2014 (\pm 2 weeks) or until the launch of Human-cl rhFVIII in the country where the study was being performed, whichever came earlier. The countries and the number of sites participating in the study was updated from about 18 centres in UK, Austria, Czech Republic, Poland, Russia, Turkey and France to 10 centres in UK, Czech Republic, Poland, Russia, France and Romania. The maximum number of patients enrolled in the study was changed from 60 to 50. Some time windows and time points of assessment were clarified. The dosing schedule was adapted to that used in the preceding GENA-03 study, i.e., the 3-times-weekly treatment schedule was added to the every-other-day treatment schedule. The name of a central laboratory in Englewood, CO, was changed from 'Esoterix Inc.' to 'LabCorp Clinical Trials.' It was clarified that not only spontaneous BEs but BEs of any cause were going to be included in the efficacy analyses. The cut-off for severe haemophilia was changed from FVIII \leq 1% to FVIII <1%. |
| 16 December 2013 | Amendment 3: only applied to France The planned clinical end of the study was moved from Q1 2014 to the time when Human-cl rhFVIII became commercially available in France, approximately by QIII 2015. All other changes included in this amendment were the same as those listed for Amendment no. 2. |
| 23 May 2014 | Amendment 4: only applied to UK Prolongation of the study duration in the UK by 3 months because by then Human-cl rhFVIII was expected to be commercially available, avoiding a switch of FVIII concentrates in this vulnerable patient population. |
| 23 May 2014 | Amendment 5: only applied to France Planned clinical end of the study was moved from QIII 2015 to the time Human-cl rhFVIII was expected to be commercially available in France, approximately by QII 2016. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported