



Clinical trial results:

Clinical Study to Investigate the Pharmacokinetics, Efficacy, Safety and Immunogenicity of human-cl rhFVIII, a Newly Developed Human Cell-Line Derived Recombinant FVIII Concentrate in Previously Treated Patients With Severe Hemophilia A.

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2008-001563-11 |
| Trial protocol | DE BG |
| Global end of trial date | 18 September 2012 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 28 December 2016 |
| First version publication date | 28 December 2016 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | GENA-01 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00989196 |
| 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) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001024-PIP01-10 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 15 February 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 September 2012 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to determine the pharmacokinetics (PK) of Human-cl rhFVIII in terms of the human coagulation factor VIII coagulant activity (FVIII:C) and to compare it with the licensed FVIII concentrate Kogenate FS in previously treated patients (PTPs) suffering from 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 several pre-specified times whether they had developed an inhibitor to factor VIII.

Background therapy:

NA

Evidence for comparator:

In part I of the study, the PK of Human-cl rhFVIII and the licensed comparator product (Kogenate FS) were assessed in a randomized, cross-over, open label manner. In part II, patients who completed Part I were followed up for a period of at least 50 exposure days (EDs) and at least 6 months during which bleeding episodes were treated with Human-cl rhFVIII only.

| | |
|---|-------------|
| Actual start date of recruitment | 27 May 2010 |
| 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 | Bulgaria: 6 |
| Country: Number of subjects enrolled | Germany: 6 |
| Country: Number of subjects enrolled | United States: 10 |
| Worldwide total number of subjects | 22 |
| EEA total number of subjects | 12 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 2 |
| Adults (18-64 years) | 19 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Recruitment period May 2010 - October 2011. In total, 22 evaluable previously-treated patients (PTPs) suffering from severe haemophilia A (FVIII:C $\leq 1\%$) were enrolled from 9 study centres in Bulgaria, Germany and the US.

Pre-assignment

Screening details:

Severe hemophilia A (FVIII:C $< 1\%$), male subjects ≥ 12 and ≤ 65 years of age, previously treated with FVIII concentrate, at least 150 EDs, Immunocompetent (CD4+ count $> 200/\mu\text{L}$), Neg. for anti-HIV, if positive viral load < 200 particles/ μL or $< 400,000$ copies/mL; freely given informed consent; no present or past inhibitor (greater/equal 0.6 BU) to FVIII

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? | No |
| Arm title | Human-cl rhFVIII vs. Kogenate FS (PK cross-over) |

Arm description:

After a FVIII wash-out period of at least 96 hours, subjects received either Human-cl rhFVIII or Kogenate FS (according to the randomisation scheme) for the first PK cycle and the other FVIII product for the second PK cycle. A dose of 50 IU FVIII /kg BW (labelled potency) was administered. PK blood samples for the determination of FVIII levels were taken before and at 0.25, 0.5, 0.75, 1, 3, 6, 9, 12, 24, 30 and 48 hours after the end of the injection.

| | |
|--|--|
| 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:

50 IU FVIII/kg BW (body weight)

| | |
|--|--|
| Investigational medicinal product name | Kogenate FS |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

50 IU FVIII/kg BW (body weight)

| | |
|------------------|---|
| Arm title | Human-cl rhFVIII (on-demand treatment of bleeding episodes) |
|------------------|---|

Arm description:

Patients who completed cross-over PK phase were followed up for a period of at least 50 exposure days (EDs) and at least 6 months and treated with Human-cl rhFVIII in case of a bleeding episode.

| | |
|----------|--------------|
| 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:

On-demand treatment: The Human-cl rhFVIII dosage (and duration) for the treatment of spontaneous or traumatic BEs depended on the location and extent of bleeding and on the clinical situation of the patient. Dosage recommendations were given for minor, moderate and major haemorrhage.

| Number of subjects in period 1 | Human-cl rhFVIII vs. Kogenate FS (PK cross-over) | Human-cl rhFVIII (on-demand treatment of bleeding episodes) |
|--------------------------------|--|--|
| | | |
| Started | 22 | 22 |
| Completed | 22 | 21 |
| Not completed | 0 | 1 |
| Lost to follow-up | - | 1 |

Baseline characteristics

Reporting groups

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

Reporting group description: -

| Reporting group values | Overall trial | Total | |
|---------------------------|---------------|-------|--|
| Number of subjects | 22 | 22 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adolescents (12-17 years) | 2 | 2 | |
| Adults (18-64 years) | 19 | 19 | |
| From 65-84 years | 1 | 1 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 22 | 22 | |

End points

End points reporting groups

| | |
|-----------------------|--|
| Reporting group title | Human-cl rhFVIII vs. Kogenate FS (PK cross-over) |
|-----------------------|--|

Reporting group description:

After a FVIII wash-out period of at least 96 hours, subjects received either Human-cl rhFVIII or Kogenate FS (according to the randomisation scheme) for the first PK cycle and the other FVIII product for the second PK cycle. A dose of 50 IU FVIII /kg BW (labelled potency) was administered. PK blood samples for the determination of FVIII levels were taken before and at 0.25, 0.5, 0.75, 1, 3, 6, 9, 12, 24, 30 and 48 hours after the end of the injection.

| | |
|-----------------------|---|
| Reporting group title | Human-cl rhFVIII (on-demand treatment of bleeding episodes) |
|-----------------------|---|

Reporting group description:

Patients who completed cross-over PK phase were followed up for a period of at least 50 exposure days (EDs) and at least 6 months and treated with Human-cl rhFVIII in case of a bleeding episode.

| | |
|----------------------------|------------------|
| Subject analysis set title | PK-PP Population |
|----------------------------|------------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

All randomised subjects who completed Phase I of the trial receiving both treatments without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results. The PK-PP population refers to the initial cross-over part of the trial.

Primary: AUC norm (FVIII:C) for Human-cl rhFVIII and Kogenate FS (Chromogenic assay)

| | |
|-----------------|--|
| End point title | AUC norm (FVIII:C) for Human-cl rhFVIII and Kogenate FS (Chromogenic assay) ^[1] |
|-----------------|--|

End point description:

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

End point timeframe:

at the end of 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: A formal statistical procedure was done to test whether the ratio of mean AUCnorm is within the 0.8 to 1.25 range. The ratio of geometric means [90% CI] for AUCnorm (Human-cl rhFVIII relative to Kogenate FS) was 0.98 [0.874, 1.107].

| End point values | PK-PP Population | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 22 | | | |
| Units: h*IU/mL (IU/kg) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Human-cl rhFVIII | 0.39 (± 0.14) | | | |
| Kogenate FS | 0.38 (± 0.09) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: AUC norm (FVIII:C) for Human-cl rhFVIII and Kogenate FS (One-stage assay)

| | |
|-----------------|--|
| End point title | AUC norm (FVIII:C) for Human-cl rhFVIII and Kogenate FS (One-stage assay) ^[2] |
|-----------------|--|

End point description:

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

End point timeframe:

at the end of 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: A formal statistical procedure was done to test whether the ratio of mean AUCnorm is within the 0.8 to 1.25 range. The ratio of geometric means [90% CI] for AUCnorm (Human-cl rhFVIII relative to Kogenate FS) was 0.97 [0.859, 1.088].

| End point values | PK-PP Population | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 22 | | | |
| Units: h*IU/mL/(IU/kg) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Human-cl rhFVIII | 0.37 (± 0.11) | | | |
| Kogenate FS | 0.38 (± 0.1) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

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.

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

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|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 15.1 |

Reporting groups

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

Reporting group description:

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

| Serious adverse events | Safety analysis population SAF | | |
|---|--------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Nervous system disorders | | | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Depression suicidal | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 4.5 %

| Non-serious adverse events | Safety analysis population SAF | | |
|---|--------------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 22 (50.00%) | | |
| Investigations | | | |
| Protein urine present | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 2 | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| urine keton body present | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Surgical and medical procedures | | | |
| Artificial crown procedure | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Dental care | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--|---------------------|--|--|
| Hypoaesthesia subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Paraesthesia subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Tremor subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| General disorders and administration site conditions Chills subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Unevaluable event subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Ear and labyrinth disorders Ear congestion subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Hypoacusis subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 2 | | |

| | | | |
|--|---------------------|--|--|
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Ascites subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Constipation subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Hepatobiliary disorders Hepatic cirrhosis subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Sinus congestion subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Psychiatric disorders Depression suicidal | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle tightness | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Periarthritis | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Impetigo | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Onychomycosis | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Tooth abscess | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 16 March 2010 | Protocol version 07, dated 16-MAR-2010 included amendments 1-3, which had been made before the study started. |
| 13 December 2010 | Protocol Amendment 04: Number of study centres and participating countries was updated due to the addition of new study centres in Germany and Bulgaria. |
| 13 April 2011 | Amendment 05: Update of planned clinical study end. Change in address of Coordinating Investigator. Addition of higher strengths of Human-cl rhFVIII Clarification of FVIII washout period prior to screening. Clarification regarding prophylactic treatments following a major surgery or certain major bleeding episodes. Update of drug supply management logistics. Clarification regarding recording of source data. Clarification regarding documentation of bleeding episodes occurring simultaneously at several sites. Update on statistical section on efficacy of the on-demand treatment. Documentation of Bleeding Episodes Occurring Simultaneously at Several Sites Statistical Analysis of Efficacy of On-Demand Treatment |
| 05 July 2012 | Amendment 06: Date for Termination of Clinical Study Address of Coordinating Investigator Responsibility for Drug Shipment to Study Centers Analysis of Inhibitor Rate |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported