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
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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.
Thoughout the study safety was assessed such as occurence 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 anaylsis population SAF

Reporting group description:

all patients exposed to treatment

Serious adverse events	Safety anaylsis 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	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Ingrowing nail			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal colic			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	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 anaylsis 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	5 / 49 (10.20%)		
occurrences (all)	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 (± 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 ≤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