Clinical trial results:
Clinical Study to Investigate the Efficacy, Safety, and Immunogenicity of human-cl rhFVIII in Previously Treated Patients With Severe Haemophilia A

Summary

EudraCT number	2009-011055-43
Trial protocol	DE AT GB
Global end of trial date	31 January 2012

Results information

Result version number	v1 (current)
This version publication date	09 October 2016
First version publication date	09 October 2016

Trial information

Trial identification

Sponsor protocol code	GENA-08

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01125813
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-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	19 July 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 January 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine in previously treated subjects suffering from severe haemophilia A the efficacy of human-cl rhFVIII during prophylactic treatment, in the treatment of bleeding episodes and in surgical prophylaxis.

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 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:

NA

Evidence for comparator:

NA

Actual start date of recruitment	22 June 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	United Kingdom: 15
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Bulgaria: 8
Country: Number of subjects enrolled	Germany: 8
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	31
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All screened 36. All enrolled 32.
Inclusion criteria: must have severe haemophilia A (FVIII:C ≤1%; historical value as documented in patient records), male patients 12 years of age or older, previously treated with FVIII concentrate, at least 150 EDs, immunocompetent (CD4+ count >200/µL), negative for anti-human HIV, freely given written ICF.

Period 1

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

Arms

Arm title	Human-cl rhFVIII

Arm description:

IMP was administerd to all patients prophylactically and for in-vivo recovery assessment and if required for treatment of bleeding episodes or surgical prophylaxis.

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:

A dose of 50 IU/kg was administered at Visit 1 and at 3 and 6 month for the purpose of assessing IVR.
Prophylactic treatment: patients received 30-40 IU FVIII/kg every other day until 6 months and at least 50 EDs had been reached.
On-demand treatment and surgical prophylaxis: dosage recommendations were given in the protocol.
The IMP was to be administered at a maximum speed of 4 mL/minute.

Number of subjects in period 1	Human-cl rhFVIII
Started	32
Completed	30
Not completed	2
Adverse event, serious fatal	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	32	32	
Age categorical Units: Subjects			
Adults (18-64 years)	31	31	
From 65-84 years	1	1	
Gender categorical Units: Subjects			
Female	0	0	
Male	32	32	

Subject analysis sets	
Subject analysis set title	ITT / Subjects on prophylactic treatment (PROPH)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients in the ITT population who received at least one prophylactic infusion.

Subject analysis set title	BLEED population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All documented bleeding episodes (BEs) of patients in the ITT population for which any amount of treatment with Human-cl rhFVIII was documented. A total of 30 BEs that were treated with Human-cl rhFVIII were recorded in 15 patients .

Subject analysis set title	SURG population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All documented surgical interventions of patients in the ITT population for which any amount of Human-cl rhFVIII prior to, during or after the surgery was documented and no other FVIII concentrate was documented within 24 hours prior to surgery.

Reporting group values	ITT / Subjects on prophylactic treatment (PROPH)	BLEED population	SURG population
Number of subjects	32	15	5
Age categorical Units: Subjects			
Adults (18-64 years)	31		5
From 65-84 years	1		0
Gender categorical Units: Subjects			
Female	0		0
Male	32		5

End points

End points reporting groups

Reporting group title	Human-cl rhFVIII

Reporting group description:

IMP was administerd to all patients prophylactically and for in-vivo recovery assessment and if required for treatment of bleeding episodes or surgical prophylaxis.

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Primary: Overall efficacy assessment of Prophylactic Treatment

End point title	Overall efficacy assessment of Prophylactic Treatment[1]

End point description:

For prophylactic treatment, primary efficacy variables were the overall efficacy assessment after a total of at least 50 EDs at the end of the study and consumption of IMP (FVIII IU/kg per month, per year) per patient and in total. Prophylactic efficacy is assessed by the monthly bleeding rate (excellent: <0.75, good: 0.75-1.0, moderate: >1.0-1.5; poor: >1.5)
Includes all bleeding episodes between start of prophylactic treatment and last prophylactic treatment + 2 days or study completion, whichever comes first. Bleeding episodes between start of treatment for surgery and re-start of prophylactic treatment after surgery are excluded.

End point type	Primary

End point timeframe:

6 month

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: descriptive analysis - no statistical analysis for this endpoint available

End point values	Human-cl rhFVIII			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Number of patients				
Excellent	29			
Good	2			
Moderate	1			
Poor	0			

Statistical analyses

No statistical analyses for this end point

Primary: Amount of Human-cl rhFVIII (IU/kg) for prophylactic treatment per month

End point title	Amount of Human-cl rhFVIII (IU/kg) for prophylactic treatment per month[2]

End point description:

End point type	Primary

End point timeframe:

Study drug consumption data per month

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: descriptive analysis - no statistical analysis for this endpoint available

End point values	ITT / Subjects on prophylactic treatment (PROPH)			
Subject group type	Subject analysis set			
Number of subjects analysed	32			
Units: Human-cl rhFVIII per month (IU/kg/month)				
arithmetic mean (standard deviation)	466.1 (± 65.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Personal efficacy assessment of treatment of bleeding episode

End point title	Personal efficacy assessment of treatment of bleeding

End point description:

At the end of a BE, the following efficacy assessment was made:
• Excellent: Abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single infusion
• Good: Definite pain relief and/or improvement in signs of bleeding within approximately 8–12 hours after an infusion requiring up to 2 infusions for complete resolution
• Moderate: Probable or slight beneficial effect within approximately 12 hours after the first infusion requiring more than two infusions for complete resolution
• None: No improvement within 12 hours, or worsening of symptoms, requiring more than 2 infusions for complete resolution

End point type	Primary

End point timeframe:

Any bleeding epsiode treated with Human-cl rhFVIII during the study

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: descriptive analysis - no statistical analysis for this endpoint available

End point values	BLEED population			
Subject group type	Subject analysis set			
Number of subjects analysed	15[4]			
Units: bleeding episodes				
Excellent	20			
Good	8			
Moderat	0			
None	0			

Notes:

[4] - Number of bleeding episodes: 28

Statistical analyses

No statistical analyses for this end point

Primary: Efficacy evaluation of the use of Human-cl rhFVIII in surgical procedures

End point title	Efficacy evaluation of the use of Human-cl rhFVIII in surgical procedures[5]

End point description:

four point scale

End point type	Primary

End point timeframe:

Overall efficacy assessment after the end of the surgical prophylactic treatment phase by the surgeon and haematologist.

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: descriptive analysis - no statistical analysis for this endpoint available

End point values	SURG population			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: Overall efficacy				
Excellent	4			
Good	1			
Moderate	0			
None	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The condition of the subject was monitored throughout the study. 24 hours SAE reporting requirement.

Adverse event reporting additional description:

All SAEs, suspected to be related to study treatment or not, were reported by telephone, fax or e-mail immediately to the responsible CPM, CRA or to local CRO.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Human-cl rhFVIII

Reporting group description:

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

Serious adverse events	Human-cl rhFVIII		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 32 (6.25%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Traumatic fracture			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Status epilepticus			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Human-cl rhFVIII		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 32 (65.63%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Paraesthesia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Diarrhea			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	6		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	4		

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 5 / 32 (15.63%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2011	• As it became clear that the study would take longer than originally anticipated, the planned clinical end was updated from Q1 2011 to Q4 2011. • In addition to vials containing 500 IU of Human-cl rhFVIII concentrate, also vials containing 1000 IU and 2000 IU were expected to become available during the study. These were included in the description of the IMP. • In this study, it was allowed to enter certain source data (vital signs, body weight and dates/times of blood drawings) directly into the CRF without prior written or electronic record of source data, turning the CRF into source. This was clarified in the text. • The final change concerned the documentation of BEs that occurred simultaneously at several sites. It was clarified that if a patient experienced simultaneously BEs at several sites, they each had to be documented as separate BEs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported