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)	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	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 ≤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/µL), 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

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Safety anaylsis population SAF

Reporting group description:

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

Serious adverse events	Safety anaylsis 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 anaylsis 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	1 / 22 (4.55%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Unevaluable event			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hypoacusis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	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. Addiition 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