Clinical trial results:
Clinical Study to Investigate the Long-Term Efficacy, Safety, and Immunogenicity of human-cl rhFVIII in Previously Treated Patients with Severe Haemophilia A – Extension Study to GENA-01

Summary

EudraCT number	2010-023242-69
Trial protocol	DE BG
Global end of trial date	30 August 2012

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-11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01341912
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 July 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 August 2012
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the long-term immunogenicity and tolerability of human-cl rhFVIII in previously treated patients with 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 pre-specified times whether they had developed an inhibitor to factor VIII.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 3
Worldwide total number of subjects	3
EEA total number of subjects	3

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)	2
From 65 to 84 years	1

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participation in this open phase 3b study was open to all patients who had completed the GENA-01 study with at least 50 exposure days (EDs) after at least 6 months of study participation.

Pre-assignment

Screening details:

NA

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:

Participation in this open phase 3b study was open to all patients who had completed the GENA-01 study with at least 50 exposure days (EDs) after at least 6 months of study participation. Overall, therefore, 21 patients would theoretically have been eligible for enrolment into GENA-11. Only 3 patients from Bulgaria participated in GENA-11 study.

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:

The dosing recommendations in GENA-11 were the same as in its predecessor study GENA-01:

• Minor haemorrhage (superficial muscle or soft tissue and oral bleeds): 20–30 IU FVIII/kg BW (body weight) every 12–24 hours until BE is resolved.
• Moderate to major haemorrhage (haemorrhage into muscles, into oral cavity; haemarthrosis; known trauma): 30–40 IU FVIII/kg BW. Repeat one dose every 12–24 hours until BE is resolved.
• Major to life-threatening BEs (intracranial, intra-abdominal, gastrointestinal or intrathoracic bleeds, central nervous system bleeds, bleeding in retropharyngeal spaces or
iliopsoas sheath, eyes/retina, fractures or head trauma): initial dose of 50–60 IUFVIII/kg BW. Repeat dose of 20–25 IU FVIII/kg BW every 8–12 hours until BE is resolved.

Number of subjects in period 1	Human-cl rhFVIII
Started	3
Completed	0
Not completed	3
Consent withdrawn by subject	3

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	3	3	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	2	2	
From 65-84 years	1	1	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	3	3	

Subject analysis sets

Subject analysis set title	BLEED population
Subject analysis set type	Safety analysis

Subject analysis set description:

The study population for which data was summarised is the BLEED population, i.e., the population of patients with documented BEs for which any amount of treatment with Human-cl rhFVIII was documented. The BLEED population in this study is identical with the safety (SAF) population, i.e., the population of patients who received at least one dose of Human-cl rhFVIII and were evaluated for AEs.

Reporting group values	BLEED population		
Number of subjects	3		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	2		
From 65-84 years	1		
85 years and over	0		

Gender categorical Units: Subjects			
Female	0		
Male	3		

End points

End points reporting groups

Reporting group title	Human-cl rhFVIII

Reporting group description:

Participation in this open phase 3b study was open to all patients who had completed the GENA-01 study with at least 50 exposure days (EDs) after at least 6 months of study participation. Overall, therefore, 21 patients would theoretically have been eligible for enrolment into GENA-11. Only 3 patients from Bulgaria participated in GENA-11 study.

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Primary: Long-term immunogenicity of Human-cl rhFVIII

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

End point description:

The long-term immunogenicity of Human-cl rhFVIII was to be assessed by determining FVIII inhibitor activity at 3-monthly intervals until study completion by the modified Bethesda assay (Nijmegen modification) using congenital FVIII-deficient human plasma spiked with Human-cl rhFVIII as a test base; anti-rhFVIII antibodies were to be measured at the same time points. An inhibitor test was considered negative if the titer was <0.6 BU.

End point type	Primary

End point timeframe:

Measurement at 3-monthly intervals until study completion

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: The original Statistical Analysis Plan (SAP) prepared for this study was amended once in response to the study being terminated prematurely. Because most of the originally planned statistical analyses would not have been significant with only 3 enrolled patients, the results of this study are summarised descriptively only.

End point values	Human-cl rhFVIII			
Subject group type	Reporting group			
Number of subjects analysed	3			
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:

Long-term clinical tolerability was assessed by monitoring AEs throughout the study.

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: The original Statistical Analysis Plan (SAP) prepared for this study was amended once in response to the study being terminated prematurely. Because most of the originally planned statistical analyses would not have been significant with only 3 enrolled patients, the results of this study are summarised descriptively only.

End point values	BLEED population			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: Occurrence of AEs				
Occurrence of AEs	0			
Occurrence of SAEs	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

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	15.0

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No AEs or SAEs occurred in any of the 3 patients.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported