Clinical trial results:
PROSPECTIVE CLINICAL STUDY IN CHILDREN WITH SEVERE HAEMOPHILIA A
TO INVESTIGATE CLINICAL EFFICACY, IMMUNOGENICITY, PHARMACOKINETICS,
AND SAFETY OF HUMAN-CL RHFVIII

Summary

EudraCT number	2010-018644-14
Trial protocol	DE AT CZ GB
Global end of trial date	06 November 2012

Results information

Result version number	v1 (current)
This version publication date	22 July 2016
First version publication date	22 July 2016

Trial information

Trial identification

Sponsor protocol code	GENA-03

Additional study identifiers

ISRCTN number	ISRCTN71212110
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	Clinical Research and Development, Octapharma Pharmazeutika Produktionsgesellschaft mbH, +43 1610320,
Scientific contact	Clinical Research and Development, Octapharma Pharmazeutika Produktionsgesellschaft mbH, +43 1610320,

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	06 November 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this clinical study was to assess clinical efficacy of Human-cl rhFVIII in terms of prevention (prophylactic treatment) and treatment of (breakthrough) BEs in previously treated children suffering from severe haemophilia A (FVIII:C <1%)

Protection of trial subjects:

This trial was conducted in accordance to the principles of GCP, ensuring that the rights, safety and well-being of patients are protected and in consistency with the Declaration of Helsinki.
Inclusion 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 AEs, lab values, vital signs and physical examinations.

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	27 December 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	Poland: 24
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	Romania: 3
Worldwide total number of subjects	59
EEA total number of subjects	41

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)	58
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period December 2010 - April 2012. PK patients in total 27 (13 patients: 2-5 years, 14 patients: 6-12 years). Non PK-patients in total 32 (16 patients 2-5 years, 16 patients 6-12 years)

Pre-assignment

Screening details:

All screened 61. All enrolled 59. Inclusion criteria: Severe haemophilia A (FVIII:C <1%);Age ≥2 to 12 years;Previously treated with FVIII concentrate (at least 50 EDs);Immunocompetence (CD4+ count >200/µL);HIV-negative or respective viral load <200 particles/µL or <400,000 copies/mL; patients had to undergo a FVIII wash-out phase of at least 72 hrs

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
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

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:

PK/recovery: 50 IU FVIII/kg body weight (BW) of the previously used FVIII concentrate followed by Human-cl rhFVIII after a wash-out period.
Prophylactic treatment: All patients were treated prophylactically: every other day or 3 times weekly. The recommended dosage regimen was 30–40 IU FVIII/kg BW. Two dose escalations of each +5 IU FVIII/kg BW were allowed in case of an inadequate response (≥2 spontaneous BEs within one month).
Treatment of breakthrough bleeding´s: dosage recommendations depending on the location and severity of the bleed are given in the protocol.
Patients were treated for at least 50 EDs and at least 6 months.

Number of subjects in period 1	Human-cl rhFVIII
Started	59
Completed	56
Not completed	3
Lack of efficacy	1
Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	59	59	
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)	58	58	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
only males participated in the clinical trial			
Units: Subjects			
Male	59	59	

End points

End points reporting groups

Reporting group title	Human-cl rhFVIII
Reporting group description:	
Prophylactic and on-demand treatment with Human-cl rhFVIII	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who received at least one dose of Human-cl rhFVIII and for whom any data was collected post treatment with Human-cl rhFVIII	
Subject analysis set title	Population of BEs (BLEED):
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All documented BEs of patients in the PROPH population for which treatment with Human-cl rhFVIII was documented. Any type of BE includes: spontaneous, traumatic, post-operative or other bleeding events.	

Primary: Efficacy of Prophylactic Treatment

End point title	Efficacy of Prophylactic Treatment[1]
End point description:	
Overall efficacy assessment	
End point type	Primary
End point timeframe:	
after 50 EDs and 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: no statistical analysis for this endpoint available

End point values	Intention-to-treat			
Subject group type	Subject analysis set			
Number of subjects analysed	59			
Units: Patients				
Excellent: Less than 0.75 spontaneous BE per month	49			
Good: Between 0.75 and 1 spontaneous BE per month	5			
Moderate: Between 1 - 1.5 spontaneous BEs / month	3			
More than 1.5 spontaneous BEs per month	1			

Statistical analyses

No statistical analyses for this end point

Primary: Frequency of BEs during prophylaxis

End point title	Frequency of BEs during prophylaxis[2]

End point description:

Monthly Rate of BEs during Prophylactic Treatment, comprises spontaneous and traumatic BEs

End point type	Primary

End point timeframe:

End of 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: no statistical analysis for this endpoint available

End point values	Intention-to-treat			
Subject group type	Subject analysis set			
Number of subjects analysed	59			
Units: Monthly Rate				
arithmetic mean (standard deviation)	0.338 (± 0.429)			

Statistical analyses

No statistical analyses for this end point

Primary: Personal efficacy assessment of treatment of bleeding episodes (four-point rating scale)

End point title	Personal efficacy assessment of treatment of bleeding episodes (four-point rating scale)[3]

End point description:

Overall efficacy assessment

End point type	Primary

End point timeframe:

All bleeding episodes treated with Human-cl rhFVIII between start and end of prophylactic treatment + 2 days or study completion, whichever comes first.

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: no statistical analysis for this endpoint available

End point values	Population of BEs (BLEED):			
Subject group type	Subject analysis set			
Number of subjects analysed	108			
Units: bleeding episodes				
Excellent: Abrupt pain relief	77			
Good: Definite pain relief	12			
Moderate: Probable or slight beneficial effect	17			
None: No improvement within 12 hours	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 hours SAE reporting requirement.
Waiver from 24 hours SAE reporting: hospitalization for the treatment of a (disease-related) BE.

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 evalutaed at each patient visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	V15.0

Reporting groups

Reporting group title	all patients exposed to treatment (safety set)

Reporting group description: -

Serious adverse events	all patients exposed to treatment (safety set)		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 59 (8.47%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
head injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
device-related infection			
alternative assessment type: Non-			

systematic			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Acute tonsillitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	all patients exposed to treatment (safety set)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 59 (64.41%)		
Injury, poisoning and procedural complications			
Head injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Injury			
alternative assessment type: Non-systematic			

subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	5		
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	5		
Chills			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Infections and infestations			
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	6		
Rhinitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	6		

Varicella			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2011	Amendment #1: The original study protocol suggested every other day prophylactic treatment with Human-cl rhFVIII for all subjects. After an enrolment period of 6 months it turned out that many patients are not willing to join the study because their doctors and parents prefer a three times weekly injection. The protocol amendment therefore specified that both - every other day treatment as well as three times weekly prophylactic treatment is allowed.
07 October 2011	Amendment #2: The original study protocol was asking for 13 evaluable patients per age cohort to undergo the pharmacokinetic (PK) investigational part of the study. This patient number was based on the EMEA-draft guideline EMEA/CHMP/BPWP/144533/2009, dated 23 July 2009, which requested 13 patients per cohort to be evaluated for the study. On 21. July 2011 the guideline has been finalized, now requesting 12 evaluable patients per age cohort to undergo the PK investigation. The protocol amendment specified that 12 evaluable PK patients per age cohort will be included into the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported