Clinical trial results:
Extension Study for Patients who completed GENA-05 (NuProtect) – to Investigate Immunogenicity, Efficacy and Safety of Treatment with Human-cl rhFVIII

Summary

EudraCT number	2013-003997-28
Trial protocol	GB DE FR
Global end of trial date	27 December 2018

Results information

Result version number	v1 (current)
This version publication date	18 July 2019
First version publication date	18 July 2019

Trial information

Trial identification

Sponsor protocol code	GENA-15

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01992549
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Octapharma Pharmazeutika Produktionsges.m.b.H.
Sponsor organisation address	Oberlaaer Strasse 235, Vienna, Austria, 1100
Public contact	sigurd.knaub@octapharma.com, Octapharma AG, +41 554512141, sigurd.knaub@octapharma.com
Scientific contact	sigurd.knaub@octapharma.com, Octapharma AG, +41 554512141, sigurd.knaub@octapharma.com

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	11 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To investigate the immunogenicity of Human-cl rhFVIII in patients who completed GENA-05 in accordance with the study protocol
• To assess the efficacy of Human-cl rhFVIII during prophylactic treatment (based on the frequency of spontaneous break-through bleeds)
• To assess the efficacy of Human-cl rhFVIII during treatment of bleeds
• To assess the efficacy of Human-cl rhFVIII in surgical prophylaxis
• To assess the safety and tolerability of Human-cl rhFVIII

Protection of trial subjects:

This trial was conducted in accordance to the principles of ICH- GCP (Note for Guidance CPMP/ICH/135/95 and national regulatory requirements, 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 risk factors associated with the investigational medicinal product.
Safety and tolerability was assessed by monitoring vital signs, standard laboratory parameters, and by monitoring adverse events (AEs)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 March 2014
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	Poland: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	India: 9
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Georgia: 4
Country: Number of subjects enrolled	Moldova, Republic of: 3
Country: Number of subjects enrolled	Ukraine: 21
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	48
EEA total number of subjects	5

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)	11
Children (2-11 years)	37
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Only patients who completed the clinical study GENA-05 in accordance with the study protocol could be enrolled.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Human-cl rhFVIII

Arm description:

Patients with Severe Haemophilia A were to be treated prophylactically or on-demand. Upon discretion of the investigator patients could be switched from on-demand to prophylactic treatment, or from prophylactic to on-demand treatment during the course of the study.

Arm type	Experimental
Investigational medicinal product name	Human cell line recombinant factor VIII
Investigational medicinal product code	Human-cl rhFVIII
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

PROPHYLACTIC TREATMENT: recommended dose of >20 IU FVIII/kg body weight. Frequency or dose adjustments could be done on Investigator's discretion. ON-DEMAND TREATMENT: recommended dose depending on location, extent of bleeding & clinical situation of the patient; for minor haemorrhage: 20-30 IU FVIII/kg BW, moderate to major haemorrhage 30-40 IU FVIII/kg BW, major to life-threatening haemorrage initial dose 50-80 IU FVIII/kg BW to achieve an intended target peak level of 100-120%. Repeat dose of >20 IUFVIII/kg BW every 6-12 hr until BE is resolved. SURGICAL PROPHYLAXIS: for minor surgeries incl. tooth extractions recommended dose: 25-30 IU FVIII/kg BW, for major surgeries: > 50 IU FVIII/kg BW within 3 hr prior to surgery to achieve an intended target peak level of approximately 100%. Repeat if necessary after 6-12 hr initially and for at least 6 -14 days until healing is complete and recurrence to regular prophylactic treatment is possible. Trough levels should be maintained at >50%.

Number of subjects in period 1	Human-cl rhFVIII
Started	48
Completed	44
Not completed	4
Serious adverse event, non-fatal	1
Lost to follow-up	2
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	48	48	
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)	11	11	
Children (2-11 years)	37	37	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	2.8		
full range (min-max)	1.3 to 11.9	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	48	48	

End points

End points reporting groups

Reporting group title	Human-cl rhFVIII

Reporting group description:

Patients with Severe Haemophilia A were to be treated prophylactically or on-demand. Upon discretion of the investigator patients could be switched from on-demand to prophylactic treatment, or from prophylactic to on-demand treatment during the course of the study.

Primary: Immunogenicity: determination of patients with positive inhibitor activity

End point title	Immunogenicity: determination of patients with positive inhibitor activity[1]

End point description:

FVIII inhibitor development was determined in BU/mL (Bethesda Units) by the modified Bethesda assay (Nijmegen modification), using congenital FVIII-deficient human plasma spiked with Human-cl rhFVIII at the timepoints described above.

No patient tested positive for inhibitors in this study.

End point type	Primary

End point timeframe:

FVIII inhibitor development determined at:
• Screening Visit • Once every 6 months during treatment phase • Study completion • Any time in case of suspicion of inhibitor development.

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: Trial includes one arm only. For statistical analysis at least 2 arms are required, so no statistical analysis can be provided. Therefore, only results for this endpoint are provided.

End point values	Human-cl rhFVIII			
Subject group type	Reporting group			
Number of subjects analysed	48[2]			
Units: Number of patients	0			

Notes:

[2] - No patient tested positive for inhibitors in this study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs and SAEs will be monitored and recorded at each visit, whether scheduled or unscheduled throughout the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Safety Population

Reporting group description:

Patients with Severe Haemophilia A were treated prophylactically or on-demand. Upon discretion of the investigator patients could be switched from on-demand to prophylactic treatment, or from prophylactic to on-demand treatment during the course of the study.

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 48 (10.42%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neuroblastoma			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Epistaxis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Varicella			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2.08 %

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 48 (60.42%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 48 (20.83%)		
occurrences (all)	16		
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			

subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	7 / 48 (14.58%)		
occurrences (all)	10		
Rhinorrhoea			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Bite			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Hand fracture			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	5		
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Diarrhoea			

subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Glossodynia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Vomiting projectile			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Hepatobiliary disorders			
Biliary dyskinesia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	2		
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	4		
Conjunctivitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		

Ear infection				
subjects affected / exposed	4 / 48 (8.33%)			
occurrences (all)	4			
Enterovirus infection				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Eye infection				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Nasopharyngitis				
subjects affected / exposed	10 / 48 (20.83%)			
occurrences (all)	12			
Otitis media				
subjects affected / exposed	2 / 48 (4.17%)			
occurrences (all)	2			
Periodontitis				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	2			
Pharyngitis				
subjects affected / exposed	4 / 48 (8.33%)			
occurrences (all)	4			
Pharyngotonsillitis				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Pulpitis dental				
subjects affected / exposed	2 / 48 (4.17%)			
occurrences (all)	2			
Respiratory tract infection				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Respiratory tract infection viral				
subjects affected / exposed	2 / 48 (4.17%)			
occurrences (all)	2			
Rhinitis				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	3			

Skin bacterial infection subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		
Staphylococcal skin infection subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		
Tonsillitis subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3		
Tracheitis subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 8		
Tracheobronchitis subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		
Viral infection subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		
Varicella subjects affected / exposed occurrences (all)	4 / 48 (8.33%) 4		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2018	• General clinical end date was fixed with 31Dec2018 • Further minor changes were implemented

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported