Clinical trial results:
Immunogenicity, Efficacy and Safety of Treatment with Human-cl rhFVIII in Previously Untreated Patients with Severe Haemophilia A

Summary

EudraCT number	2012-002554-23
Trial protocol	GB PL DE ES FR PT SI HR IT
Global end of trial date	24 March 2020

Results information

Result version number	v1 (current)
This version publication date	23 August 2020
First version publication date	23 August 2020

Trial information

Trial identification

Sponsor protocol code	GENA-05

Additional study identifiers

ISRCTN number	ISRCTN50040185
ClinicalTrials.gov id (NCT number)	NCT01712438
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Octapharma AG
Sponsor organisation address	Seidenstrasse 2, Lachen, Switzerland, CH-8853
Public contact	Sigurd Knaub, Octapharma AG, 0041 55 451 21 41, sigurd.knaub@octapharma.com
Scientific contact	Sigurd Knaub, Octapharma AG, 0041 55 451 21 41, sigurd.knaub@octapharma.com

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 March 2020
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 100 PUPs suffering from severe haemophilia A (FVIII:C < 1%).

Protection of trial subjects:

This trial was conducted in accordance to the principles of ICH- GCP, ensuring that the rights, safety and well-being of patients are protected and in consistency with the Declaration of Helsinki, national regulatory requirements and FDA Code of Federal Regulations.
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.
Clinical safety and tolerability was assessed by monitoring vital signs, adverse events and safety laboratory parameters, including inhibitors against FVIII.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Slovenia: 1
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Belarus: 3
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Georgia: 6
Country: Number of subjects enrolled	India: 13
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Moldova, Republic of: 4
Country: Number of subjects enrolled	Morocco: 4
Country: Number of subjects enrolled	Russian Federation: 2

Country: Number of subjects enrolled	Ukraine: 30
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	108
EEA total number of subjects	33

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	1
Infants and toddlers (28 days-23 months)	79
Children (2-11 years)	26
Adolescents (12-17 years)	2
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:

Patients with documented diagnosis Severe Haemophilia A with no previous treatment with FVIII concentrates or other blood products containing FVIII were screened according to predefined in- and exclusion criteria.

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:

Prophylactic treatment was recommended, but finally, it was the decision of the responsible treating physician whether patients were treated prophylactically or on demand. Patients could switch 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-cl rhFVIII
Investigational medicinal product code	
Other name	Nuwiq
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The decision whether to treat patients prophylactically or on-demand was always at the discretion of the treating physician.
Prophylactic treatment: Recommended dose 20-50 IU FVIII/kg body weight (BW).
On-demand treatment: Dosage and duration of treatment of spontaneous or traumatic bleeds depended on the location and the extent of bleeding as well as on the clinical situation of the patient.
Recommended doses: 20-30 IU FVIII/kg BW (minor haemorrhage), 30-40 IU FVIII/kg BW (moderate to major haemorrhage) or 40-60 IU FVIII/kg BW (major to life-threatening haemorrhage).
Surgical prophylaxis: depended on the type of surgery and the patient's individual incremental FVIII recovery. Recommended doses: 25-30 IU FVIII/kg BW (minor surgeries) or 40-60

Number of subjects in period 1	Human-cl rhFVIII
Started	108
Completed	85
Not completed	23
98 EDs	1
refuse to continue	1
non-compliance with protocol	1
sponsor request/ study ending	2
Switch to other product	2

unwilling to perform visit	1
Consent withdrawn by subject	4
family moving	1
FVIII positive but no ITI	3
Adverse event, non-fatal	1
Therapy Failure	3
Protocol Violation	1
Lost to follow-up	1
no real severe HA, not reached 100 ED	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	108	108	
Age categorical Units: Subjects			
<1 month	1	1	
1-6 months	9	9	
6-12 months	47	47	
>12 months	51	51	
Age continuous Units: months			
arithmetic mean	21.6		
full range (min-max)	0 to 146	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	108	108	

End points

End points reporting groups

Reporting group title	Human-cl rhFVIII
Reporting group description:	
Prophylactic treatment was recommended, but finally, it was the decision of the responsible treating physician whether patients were treated prophylactically or on demand. Patients could switch from on-demand to prophylactic treatment, or from prophylactic to on-demand treatment during the course of the study.	
Subject analysis set title	Safety Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects who received at least one dose of Human-cl rhFVIII	
Subject analysis set title	ITT
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects who received at least one dose of Human-cl rhFVIII.	
Subject analysis set title	PROPH
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects in the ITT population who have at least one prophylactic treatment.	
Subject analysis set title	BLEED Population
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects that received any amount of Human-cl rhFVIII for a bleeding episode	
Subject analysis set title	SURG Population
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects that received any amount of Human-cl rhFVIII for surgical prophylaxis during a total of 26 surgeries.	
Subject analysis set title	n (BE)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Number of Bleeding Events in BLEED population during inhibitor-free periods n=804	
Subject analysis set title	Percentage (%)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Percentage of BE in BLEED population during inhibitor-free periods (n=804)	
Subject analysis set title	Minor Surgeries
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Minor Surgeries	
Subject analysis set title	Major Surgeries
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Major surgery	

Primary: Immunogenicity: Incidence of Human-cl rhFVIII Inhibitors

End point title	Immunogenicity: Incidence of Human-cl rhFVIII Inhibitors[1]
End point description:	
The primary endpoint of this study was the evaluation of FVIII-inhibitor development (in previously untreated patients) treated with Human-cl rhFVIII. An inhibitor was assessed positive if the modified	

Bethesda assay (Nijmegen modification) as measured in a central lab and confirmed from a second sample resulted in a titre ≥0.6 BU/mL at any time point during the observation period. The definitions for thresholds were ≥0.6 to <5 BU/mL for a "low titre" inhibitor and ≥5 BU/mL for a "high-titre" inhibitor.

End point type	Primary

End point timeframe:

maximum of 5 years (100 exposure days)

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 statistical analysis of the primary, secondary and safety endpoints is to be understood in the exploratory sense. Therefore no confirmative statistical analysis was done and statistical analyses are descriptive only.

End point values	Safety Analysis Population			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Participants				
number (not applicable)				
High titre inhibitor (>5 BU/mL)	17			
High titre inhibitor (>5 BU/mL) %	16.2			
Low titre inhibitor (<5 BU/mL)	11			
Low titre inhibitor (<5 BU/mL) %	10.5			
Any inhibitor (>0.6 BU/mL)	28			
Any inhibitor (>0.6 BU/mL) %	26.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Monthly Spontaneous Break-through Bleeds

End point title	Frequency of Monthly Spontaneous Break-through Bleeds

End point description:

The monthly bleeding rate (MBR) was calculated during inhibitor-free periods for spontaneous bleeding events (BEs) during prophylactic treatment with Human cl rhFVIII

End point type	Secondary

End point timeframe:

Up to a maximum 5 years (100 exposure days)

End point values	PROPH			
Subject group type	Subject analysis set			
Number of subjects analysed	103			
Units: MBR				
arithmetic mean (confidence interval 95%)	0.080 (0.035 to 0.125)			

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy of Human-cl rhFVIII for the Treatment of Bleeds

End point title	Efficacy of Human-cl rhFVIII for the Treatment of Bleeds

End point description:

The efficacy assessment of bleeding episodes at end of a BE was evaluated on an objective four-point scale by the patient's parent(s)/legal guardian(s) together with the Investigator in case of on-site treatment.

End point type	Secondary

End point timeframe:

At end of a BE

End point values	n (BE)	Percentage (%)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	100		
Units: BE				
number (not applicable)				
Excellent	510	63.4		
Good	237	29.5		
Moderate	51	6.3		
None	6	0.7		
Total number of assessed BE	804	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy of Human-cl rhFVIII for Surgical Prophylaxis

End point title	Efficacy of Human-cl rhFVIII for Surgical Prophylaxis

End point description:

Overall efficacy assessment based on objective 4-point scales (excellent, good, moderate, none) performed jointly by the haematologist and surgeon.

End point type	Secondary

End point timeframe:

At the conclusion of the post-operative phase (ie until ≥ 2 (minor surgeries) or ≥ 6 days post-surgery (major surgeries), until healing is complete and the subject returned to his regular treatment).

End point values	SURG Population	Minor Surgeries	Major Surgeries	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	24	13	11	
Units: Number of surgeries assessed				
number (not applicable)				
Excellent	15	7	8	
Excellent (%)	71.4	70.0	72.7	
Good	3	1	2	
Good (%)	14.3	10.0	18.2	
Moderate	2	1	1	
Moderate (%)	9.5	10.0	9.1	
None	1	1	0	
None (%)	4.8	10.0	0.0	
missing	5	5	0	
Total	21	10	11	
Total (%)	100.0	100.0	100.0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The frequency of AEs, as monitored throughout the whole study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Safety Population (SAF)

Reporting group description: -

Serious adverse events	Safety Population (SAF)		
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 108 (44.44%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	2 / 108 (1.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Injury			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Limb injury			

subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Scrotal haematoma			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin injury			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Subdural haemorrhage			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic haematoma			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haematoma			
subjects affected / exposed	4 / 108 (3.70%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Factor IX inhibition			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Factor VIII inhibition	Additional description: 2 FVIII inhibitor relapses during ITI Therapy.		
subjects affected / exposed	28 / 108 (25.93%)		
occurrences causally related to treatment / all	30 / 30		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic anaemia			
subjects affected / exposed	2 / 108 (1.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 108 (4.63%)		
occurrences causally related to treatment / all	4 / 8		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mouth haemorrhage			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Apnoea			

subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	2 / 108 (1.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Joint swelling			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	2 / 108 (1.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	2 / 108 (1.85%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Ear infection			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Fungal skin infection			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	2 / 108 (1.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Periodontitis			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 108 (1.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Septic shock			

subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device issue			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety Population (SAF)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 108 (89.81%)		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 108 (19.44%)		
occurrences (all)	28		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed occurrences (all)	60 / 108 (55.56%) 131		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Teething subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 14 / 108 (12.96%) 20 10 / 108 (9.26%) 11 11 / 108 (10.19%) 23		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 15 / 108 (13.89%) 29		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 11 / 108 (10.19%) 14		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Ear infection subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Laryngitis subjects affected / exposed occurrences (all)	 11 / 108 (10.19%) 18 11 / 108 (10.19%) 20 10 / 108 (9.26%) 10 7 / 108 (6.48%) 9 6 / 108 (5.56%) 9		

Nasopharyngitis			
subjects affected / exposed	34 / 108 (31.48%)		
occurrences (all)	72		
Respiratory tract infection			
subjects affected / exposed	7 / 108 (6.48%)		
occurrences (all)	11		
Rhinitis			
subjects affected / exposed	20 / 108 (18.52%)		
occurrences (all)	37		
Upper respiratory tract infection			
subjects affected / exposed	12 / 108 (11.11%)		
occurrences (all)	20		
Varicella			
subjects affected / exposed	8 / 108 (7.41%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2012	Amendment 1: • Safety laboratory: clarification regarding the timing of safety laboratory testing. • ITI patient follow-up: clarification regarding baseline FVIII inhibitor level determination, recovery time-points, and half-life evaluation. One hour time-point was found to be redundant and was deleted in the schedule table. • Definition/classification of haemorrhages: clarification regarding specification of haemorrhage classification. • Washout period specification: clarification regarding washout prior to follow-up visits. • Adverse events: Correction of safety assessments, adding that AEs and SAEs were to be monitored and recorded throughout the study. • Classification of ADRs: Addressed request asking to further specify the definition regarding expected ADRs. • Specification of blood volume limits: Addressed request asking to further specify the definition regarding the blood volume limits for sampling in neonates. • Definition of PP population: clarification regarding definition of PP population.
30 September 2013	Amendment 2: • IMP vial handling: general clarification. • Adaptation of ITI: adaption to comply with international ITI target criteria. • Overall efficacy assessment: clarification regarding the overall efficacy assessment to be done by the surgeon and haematologist together. • Safety laboratory parameter time points: correction of the time points for testing of safety laboratory parameters. • Home treatment with IMP: clarification that IMP for home use would be provided in cooling boxes, if appropriate. • Follow-up visits: clarification regarding timing of the follow-up visits. • Measurement of vital signs after IMP treatment at study site: changes were made to the schedule for measuring vital signs, allowing some flexibility for parents/patients in terms of avoiding unnecessary waiting times at the study site after IMP administration. • RNA Expression Analysis: further specification of the time point of RNA expression analysis was added. • Epitope mapping during ITI follow-up: the time point of epitope mapping analysis was added. • Administration of IMP at home: it was clarified that nurses could also administer IMP at home. • Efficacy assessment specification: A clarification/correction was implemented specifying that the post-operative efficacy assessment was performed by the haematologist only. • Serious adverse event (SAE) reporting: additional reporting line was added. • Epitope mapping – blood collection volume and time-points: additional specifications and corrections were made in connection with the change of the central laboratory responsible for Epitope mapping. • Laboratory change: the central laboratory for Epitope mapping was changed.

11 November 2014	Amendment 3: • Study duration: study duration was updated • Dose recommendation for prophylactic/on-demand/surgical prophylactic treatment: the dose recommendations were adapted to those from the approved SmPC for the marketed product (Nuwiq). • Statistical methods and sample size: the first of 2 interim analyses was cancelled since this was not an authority requirement. The second analysis (reported in the interim report) was to be performed as requested by the respective EMA guideline. • Dose rationale for starting dose: the dose recommendations were adapted to those from the approved SmPC for the marketed product (Nuwiq). • Safety and tolerability, and safety lab test specification: additional clarification, including more detailed description of the standard laboratory parameters. • Withdrawal and replacement of patients: a more detailed implementation of the respective EMA guideline with the clarification that patients were not to be replaced only if they had received more than 50 exposures with the IMP. • Dose and dosing schedule: correction made. Dose and dosing schedule: Immune Tolerance Induction: additional clarification, including specification that patients who do not start ITI within 1 year after inhibitor detection are withdrawn from the study. • Study conduct: observations per visit: additional clarification that F8 gene mutation analysis is mandatory but could be performed later in the study. • Data handling and record keeping: documentation of data: general clarification.
01 February 2018	Amendment 4: • The study completion timeline was clarified. It was stated that the study would be completed in the 4th quarter 2018 for all patients, except those continuing ITI treatment. • Optional retrospective analysis of blood samples for epitope mapping was introduced in patients who developed an inhibitor against FVIII and started an ITI plus in an inhibitor negative control group. • For health economic parameters, more clarity on information collected from patients' parents was provided. • More clarity on information collected towards patient demographics during screening visit was provided.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported