Clinical trial results:
Prospective, open-label, multicentre phase 3b study to assess the efficacy and safety of personalized prophylaxis with Human-cl rhFVIII in previously treated adult patients with severe haemophilia A

Summary

EudraCT number	2014-002986-30
Trial protocol	FR NL FI SI HR
Global end of trial date	05 September 2018

Results information

Result version number	v1 (current)
This version publication date	08 November 2019
First version publication date	08 November 2019

Trial information

Trial identification

Sponsor protocol code	GENA-21b

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02256917
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: BB-IND 13722

Notes:

Sponsors

Sponsor organisation name	Octapharma AG
Sponsor organisation address	Seidenstrasse 2, Lachen, Switzerland, CH-8853
Public contact	Sigurd Knaub, Octapharma AG, +41 (0)55 451 21 41, sigurd.knaub@octapharma.com
Scientific contact	Sigurd Knaub, Octapharma AG, +41 (0)55 451 21 41, 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	01 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the annualised total bleeding rate (ABR) of individually tailored prophylaxis with the historical bleeding rate observed in patients having received on-demand treatment with Human-cl rhFVIII from clinical study GENA-01

Protection of trial subjects:

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and ICH-GCP (Note for Guidance CPMP/ICH/135/95), and national regulatory requirements. 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. Throughout the study safety was assessed, such as occurrence of AEs, documentation of concomitant medication and testing for FVIII inhibitor formation.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	13 May 2015
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	Netherlands: 2
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	Croatia: 2
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 4
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	58
EEA total number of subjects	16

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)	57
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients with severe haemophilia A (FVII:<1%) having previous treatment with any FVIII product for at least 150 exposure days were screened according to predefined in- and exclusion criteria. Patients in Japan who completed the 6 months of prophylactic treatment in Treatment Phase II were given the option to continue in a Sub-Study Extension Phase

Period 1

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

Arms

Arm title	Initial PK Assessment

Arm description:

At the Initial PK Visit, patients were to receive Human-cl rhFVIII at a dose of 60 ± 5 IU/kg (labelled dose).

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:

At the Initial PK Visit, patients were to receive Human-cl rhFVIII at a dose of 60 ± 5 IU/kg (labelled dose)

Number of subjects in period 1	Initial PK Assessment
Started	58
Completed	58

Period 2

Period 2 title	Prophylactic Treatment—Phase I
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Prophylactic Treatment—Phase I

Arm description:

The 72-hour sampling time point of the Initial PK Visit marked the beginning of Prophylactic Treatment—Phase I, in which patients were to be treated prophylactically every other day or 3x/week with a dose of 30–40 IU/kg BW for about 1–3 months until PK data had been analysed and discussed with the investigator. Dose escalations were allowed in case of an inadequate frequency and severity of breakthrough bleeding episodes in accordance with the institution's standard clinical care. The maximum dose for a single infusion was 45 IU/kg BW in Japan.

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:

Patients were to be treated prophylactically every other day or 3x/week with a dose of 30–40 IU/kg BW for about 1–3 months until PK data had been analysed and discussed with the investigator. Dose escalations were allowed in case of an inadequate frequency and severity of breakthrough bleeding episodes in accordance with the institution's standard clinical care. The maximum dose for a single infusion was 45 IU/kg BW in Japan

Number of subjects in period 2	Prophylactic Treatment—Phase I
Started	58
Completed	56
Not completed	2
Withdrawl by patient	2

Period 3

Period 3 title	Prophylactic Treatment—Phase II
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Prophylactic Treatment—Phase II

Arm description:

Patients were to be treated prophylactically for 6 months. Prophylactic doses and dosing intervals were recommended by the Sponsor for each patient based on the analysis of individual PK data obtained at the Initial PK Visit with the one-stage assay.

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:

Based on an appropriate PK model, various dosing intervals (usually 12-hr intervals) and corresponding doses (in IU/kg) were calculated, which hypothetically lead to FVIII:C plasma concentrations of at least 0.01 IU/mL at the end of the respective injection interval. The goal was to use the maximum regular prophylactic dosing interval that could be achieved with a maximum dose of not more than 65 IU/kg and that maintained a trough level of ≥0.01 IU/mL.
At the 4-Month Visit the dose per injection for the remainder of the study could have been reduced provided that FVIII:C trough levels (one-stage assay) obtained at the 2-Month Visit were ≥0.01 IU/mL and that the patient had not experienced any spontaneous bleed up to the 4-Month Visit.In case of unacceptable frequent and/or severe spontaneous breakthrough bleedings, the dose was to be increased by approximately 5 IU/kg . The maximum dose was preferably not to exceed 65 IU/kg.

Number of subjects in period 3	Prophylactic Treatment—Phase II
Started	56
Completed	52
Not completed	4
Stopped on his own account	1
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	58	58	
Age categorical Units: Subjects			
Adults (18-64 years)	57	57	
From 65-84 years	1	1	
Age continuous Units: years			
median	36.5		
full range (min-max)	18 to 71	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	58	58	

End points

End points reporting groups

Reporting group title	Initial PK Assessment
Reporting group description:	
At the Initial PK Visit, patients were to receive Human-cl rhFVIII at a dose of 60 ± 5 IU/kg (labelled dose).	
Reporting group title	Prophylactic Treatment—Phase I
Reporting group description:	
The 72-hour sampling time point of the Initial PK Visit marked the beginning of Prophylactic Treatment—Phase I, in which patients were to be treated prophylactically every other day or 3x/week with a dose of 30–40 IU/kg BW for about 1–3 months until PK data had been analysed and discussed with the investigator. Dose escalations were allowed in case of an inadequate frequency and severity of breakthrough bleeding episodes in accordance with the institution's standard clinical care. The maximum dose for a single infusion was 45 IU/kg BW in Japan.	
Reporting group title	Prophylactic Treatment—Phase II
Reporting group description:	
Patients were to be treated prophylactically for 6 months. Prophylactic doses and dosing intervals were recommended by the Sponsor for each patient based on the analysis of individual PK data obtained at the Initial PK Visit with the one-stage assay.	
Subject analysis set title	GENA-01 (ITT)
Subject analysis set type	Full analysis
Subject analysis set description:	
ITT population in the GENA-01 study	
Subject analysis set title	GENA-21b (PROPH)
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients in the ITT population who enter the Prophylactic Treatment—Phase II of the study (i.e., have at least one prophylactic treatment in Phase II)	
Subject analysis set title	GENA-01 (PP)
Subject analysis set type	Full analysis
Subject analysis set description:	
PP- population of GENA-01 study	
Subject analysis set title	GENA-21b (PROPH-PP)
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients in the PP population who enter the Prophylactic Treatment—Phase II of the study – who have evaluable initial PK results for the evaluation of the individual prophylactic treatment schedule – with at least 6 months (–2 weeks) of individual prophylactic treatment (Prophylactic Treatment—Phase II) with Human-cl rhFVIII – who have no significant dosing or treatment errors, e.g., several unexplained interruptions of individual prophylaxis with Human-cl rhFVIII, e.g. >20% of prophylactic injections were not given within the prescribed treatment intervals (± 1 day)	
Subject analysis set title	GENA-01 vs GENA-21b
Subject analysis set type	Full analysis
Subject analysis set description:	
Comparison of ABRs between GENA-01 (N=56) and GENA-21b (N=22)	
Subject analysis set title	PK-PP Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The PK-PP population contained all patients in the PK analysis population who completed the initial PK sampling phase of the trial without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results.	
Subject analysis set title	SAF-Population

Subject analysis set type	Safety analysis

Subject analysis set description:

The SAF population included 58 patients who received at least one infusion of Human-c1 rhFVIII in the GENA-21b trial

Primary: Annualized Total Bleeding Rate of Individually Tailored Prophylaxis

End point title	Annualized Total Bleeding Rate of Individually Tailored Prophylaxis[1]

End point description:

The analysis population comprised 56 patients who received at least one infusion of Human-cI rhFVIII for individualized prophylaxis in the GENA-21b trial. Their annualized bleeding rate (ABR) was compared with those in patients from the completed GENA-01 trial who received only on-demand treatment.
A respective confirmative one-sided one-sample Poisson-test was used to demonstrate if the mean ABR in patients with individually tailored prophylaxis is at least 50% below the mean ABR rate in the GENA-01 trial. (95% CI (2-Sided) 95% 4.06 to 5.79)
A confidence interval of 97.5% for confirmative analysis was also used - the respective upper and lower limit CIs were 3.96-5.93

End point type	Primary

End point timeframe:

6 months

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 has 1 arm only. For entry of statistical analysis at least 2 arms are required, therefore only results for this endpoint are provided. Prim. endpoint was reduction of the ABR in the GENA-01 on-demand study by 50% during individually tailored prophylaxis. The primary endpoint was met, as the confirmative one-sided one-sample Poisson-test demonstrated that the mean ABR in patients with individually tailored prophylaxis (4.87) was at least 50% below the mean ABR rate in GENA-01 trial (49.36).

End point values	GENA-01 (ITT)	GENA-21b (PROPH)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	56		
Units: Mean ABR				
number (not applicable)				
Annualized Bleeding Rate (ABR)	49.36	4.87		

Statistical analyses

No statistical analyses for this end point

Primary: Annualised Total Bleeding Rate of Individually Tailored Prophylaxis

End point title	Annualised Total Bleeding Rate of Individually Tailored Prophylaxis[2]

End point description:

GENA-21b: Number of bleeding episodes / (time in days of the period - days of surgery phases) x 365.25 days.
GENA-01: Number of bleeding episodes / (time in days of the period) x 365.25 days

Mean ABR per patient was 4.67 in the GENA-21b PROPH population and 58.08 in the GENA-01 ITT population.

End point type	Primary

End point timeframe:

6 months

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: Trial has 1 arm only. For entry of statistical analysis at least 2 arms are required, therefore only results for this endpoint are provided. Results for this endpoint are presented as mean only. No statistical analysis performed for this endpoint.

End point values	GENA-01 (ITT)	GENA-21b (PROPH)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	56		
Units: ABR				
number (not applicable)				
Mean Annualised Total Bleeding Rate	58.08	4.67		
± SD	30.78	6.46		
95% CI for mean lower	44.43	2.94		
95% CI for mean upper	71.73	6.40		
Median	54.5	2.04		
Median range lower	9.4	0		
Median range upper	129.8	26.8		

Statistical analyses

No statistical analyses for this end point

Primary: Comparison of Annualised Total Bleeding Rates (Negative Binomial Regression Model)

End point title	Comparison of Annualised Total Bleeding Rates (Negative Binomial Regression Model)[3]

End point description:

Reduction of the annualized total bleeding rate (ABR) observed in the GENA-01 study vs. GENA-21B analyzed with a Negative Binomial regression model including a correction for overdispersion.

End point type	Primary

End point timeframe:

6 months

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: Trial has 1 arm only. For entry of statistical analysis at least 2 arms are required, therefore only results for this endpoint are provided. Reduction of the annualized total bleeding rate (ABR) observed in the GENA-01 study vs. GENA-21B analyzed with a Negative Binomial regression model including a correction for overdispersion.

End point values	GENA-01 vs GENA-21b			
Subject group type	Subject analysis set			
Number of subjects analysed	56			
Units: Rate ratio				
number (not applicable)				
Rate ratio	11.89			
95% CI lower limit	7.50			

95% CI upper limit	18.86			
p-value (2-sided) <	0.0001			

Statistical analyses

No statistical analyses for this end point

Primary: Comparison of Annualised Total Bleeding Rates (Poisson Regression Model)

End point title	Comparison of Annualised Total Bleeding Rates (Poisson Regression Model)[4]

End point description:

Reduction of the annualized total bleeding rate (ABR) observed in the GENA-01 study vs. GENA-21B analyzed with a Poisson regression model including a correction for overdispersion.

End point type	Primary

End point timeframe:

6 months

Notes:

[4] - 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 has 1 arm only. For entry of statistical analysis at least 2 arms are required, therefore only results for this endpoint are provided. Reduction of the annualized total bleeding rate (ABR) observed in the GENA-01 study vs. GENA-21B analyzed with a Poisson regression model including a correction for overdispersion.

End point values	GENA-01 vs GENA-21b			
Subject group type	Subject analysis set			
Number of subjects analysed	56			
Units: Rate Ratio				
number (not applicable)				
Rate ratio	10.14			
95% CI lower limit	6.12			
95% CI upper limit	16.80			
p-value (2-sided) <	0.0001			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Spontaneous Bleeding Rate of Individually Tailored Prophylaxis

End point title	Annualized Spontaneous Bleeding Rate of Individually Tailored Prophylaxis

End point description:

The confirmative one-sided one-sample Poisson-test demonstrated that the mean spontaneous ABR in patients with individually tailored prophylaxis (3.12) is at least 50% below the mean spontaneous ABR rate in the GENA-01 trial (32.23). Two-sided 95% confidence interval for parameter of Poisson distribution.

ABR = Sum of BEs / Sum of time periods under risk.

End point type	Secondary

End point timeframe:

6 months

End point values	GENA-21b (PROPH)			
Subject group type	Subject analysis set			
Number of subjects analysed	56			
Units: ABR				
number (not applicable)				
Annualized Spontaneous Bleeding Rate (ABR)	3.12			
95% CI for ABR lower limit	2.48			
95% CI for ABR upper limit	3.87			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Spontaneous Bleeding Rate of Individually Tailored Prophylaxis

End point title	Annualized Spontaneous Bleeding Rate of Individually Tailored Prophylaxis

End point description:

Spontaneous annualized bleeding rate (ABR) of individually tailored prophylaxis (GENA-21b) compared to historical bleeding rate in patients having received on-demand treatment (GENA-01) with Human-cl rhFVIII.
The analysis population comprised 56 patients who received at least one infusion of Human-cI rhFVIII for individualized prophylaxis in the GENA-21b trial. Their annualized spontaneous bleeding rate was compared with those in patients from the completed GENA-01 trial who received only on-demand treatment.

End point type	Secondary

End point timeframe:

6 months

End point values	GENA-01 (ITT)	GENA-21b (PROPH)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	56		
Units: ABR				
number (not applicable)				
Mean Annualised Spontaneous Bleeding Rate	38.46	2.98		
± SD	28.07	5.76		
95% CI for mean lower	26.01	1.43		
95% CI for mean upper	50.90	4.52		

Median	40.6	0		
Median range lower	0	0		
Median range upper	99.3	25.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Total Bleeding Rate in Patients With 2x/Week (or Less) Prophylaxis

End point title	Annualized Total Bleeding Rate in Patients With 2x/Week (or Less) Prophylaxis

End point description:

A respective confirmative one-sided one-sample Poisson-test was used to demonstrate if the mean ABR in patients with 2x/week prophylaxis or less with individually tailored prophylaxis is at least 50% below the mean ABR rate in the GENA-01 trial

End point type	Secondary

End point timeframe:

6 months

End point values	GENA-21b (PROPH)			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: ABR				
number (not applicable)				
Annualised Total Bleeding Rate	5.03			
95% CI for ABR lower limit	3.90			
95% CI for ABR upper limit	6.39			
97.5% CI for ABR lower limit	3.76			
97.5% CI for ABR upper limit	6.60			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised Total Bleeding Rates in Patients with 2x/Week Prophylaxis or Less

End point title	Annualised Total Bleeding Rates in Patients with 2x/Week Prophylaxis or Less

End point description:

The analysis population comprised 29 patients who received at least one infusion of Human-cI rhFVIII for individualized prophylaxis in the GENA-21b trial at intervals of 2x/week or less. Their annualized spontaneous bleeding rate was compared with those in patients from the completed GENA-01 trial who received only on-demand treatment.

End point type	Secondary

End point timeframe:

6 months

End point values	GENA-01 (ITT)	GENA-21b (PROPH)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	29		
Units: ABR				
number (not applicable)				
Mean Annualised Total Bleeding Rate	58.08	4.82		
± SD	30.78	6.98		
95% CI for mean lower	44.43	2.16		
95% CI for mean upper	71.73	7.47		
Median	54.5	2.0		
Median range lower	9.4	0		
Median range upper	129.8	26.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Prophylactic Dosing Interval

End point title	Median Prophylactic Dosing Interval

End point description:

Means and medians over median actual dosing intervals between two prophylactic treatments per patient. The analysis population comprised 56 patients who received at least one infusion of Human-cI rhFVIII for individualized prophylaxis in the GENA-21b trial.

End point type	Secondary

End point timeframe:

6 months

End point values	GENA-21b (PROPH)			
Subject group type	Subject analysis set			
Number of subjects analysed	56			
Units: Hours				
number (not applicable)				
Median interval between prophylactic doses	83.9			
Mean interval between prophylactic doses	82.2			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC divided by the dose (AUCnorm) of Human-cl rhFVIII

End point title	AUC divided by the dose (AUCnorm) of Human-cl rhFVIII

End point description:

AUCnorm of Human-cl rhFVIII measured using the one-stage (OS) assay. The PK-PP population contained all patients in the PK analysis population who completed the initial PK sampling phase of the trial without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results.

End point type	Secondary

End point timeframe:

Before injection (within 1 h before injection) and up to 72 h (± 2 h) after the end of injection.

End point values	PK-PP Population			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: AUCnorm				
arithmetic mean (standard deviation)				
Mean	0.302 (± 0.116)			

Statistical analyses

No statistical analyses for this end point

Secondary: In-vivo Recovery (IVR) of Human-cl rhFVIII

End point title	In-vivo Recovery (IVR) of Human-cl rhFVIII

End point description:

IVR of Human-cl rhFVIII measured using the one-stage (OS) assay. The PK-PP population contained all patients in the PK analysis population who completed the initial PK sampling phase of the trial without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results.

End point type	Secondary

End point timeframe:

Before injection (within 1 h before injection) and up to 72 h (± 2 h) after the end of injection.

End point values	PK-PP Population			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: IVR				
arithmetic mean (standard deviation)	1.775 (± 0.421)			

Statistical analyses

No statistical analyses for this end point

Secondary: Half Life (t1/2) of Human-cl rhFVIII

End point title	Half Life (t1/2) of Human-cl rhFVIII

End point description:

T1/2 of Human-cl rhFVIII measured using the one-stage (OS) assay. The PK-PP population contained all patients in the PK analysis population who completed the initial PK sampling phase of the trial without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results.

End point type	Secondary

End point timeframe:

Before injection (within 1 h before injection) and up to 72 h (± 2 h) after the end of injection.

End point values	PK-PP Population			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: t1/2				
arithmetic mean (standard deviation)	15.725 (± 4.029)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time (MRT) of Human-cl rhFVIII

End point title	Mean Residence Time (MRT) of Human-cl rhFVIII

End point description:

MRT of Human-cl rhFVIII measured using the one-stage . The PK-PP population contained all patients in the PK analysis population who completed the initial PK sampling phase of the trial without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results.

End point type	Secondary

End point timeframe:

Before injection (within 1 h before injection) and up to 72 h (± 2 h) after the end of injection

End point values	PK-PP Population			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: MRT				
arithmetic mean (standard deviation)	20.762 (± 5.997)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (CL) of Human-cl rhFVIII

End point title	Clearance (CL) of Human-cl rhFVIII

End point description:

CL of Human-cl rhFVIII measured using the one-stage (OS) assay. The PK-PP population contained all patients in the PK analysis population who completed the initial PK sampling phase of the trial without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results.

End point type	Secondary

End point timeframe:

Before injection (within 1 h before injection) and up to 72 h (± 2 h) after the end of injection.

End point values	PK-PP Population			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: CL				
arithmetic mean (standard deviation)	3.859 (± 1.670)			

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution at Steady State (Vss) Human-cl rhFVIII

End point title	Volume of Distribution at Steady State (Vss) Human-cl rhFVIII

End point description:

Vss of Human-cl rhFVIII measured using the one-stage (OS) assay. The PK-PP population contained all patients in the PK analysis population who completed the initial PK sampling phase of the trial without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results.

End point type	Secondary

End point timeframe:

Before injection (within 1 h before injection) and up to 72 h (± 2 h) after the end of injection.

End point values	PK-PP Population			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: Vss				
arithmetic mean (standard deviation)	72.901 (± 16.454)			

Statistical analyses

No statistical analyses for this end point

Secondary: Usage of Human-cl rhFVIII (FVIII IU/kg bw Per Week Per Patient)

End point title	Usage of Human-cl rhFVIII (FVIII IU/kg bw Per Week Per Patient)

End point description:

Average weekly consumption of Human-cl rhFVIII reported as IU/kg bw per week per patient was determined during individualized prophylactic treatment. The analysis population comprised 56 patients who received at least one infusion of Human-cI rhFVIII for individualized prophylaxis in the GENA-21b trial.

End point type	Secondary

End point timeframe:

6 months

End point values	GENA-21b (PROPH)			
Subject group type	Subject analysis set			
Number of subjects analysed	56			
Units: FVIII IU/kg bw Per Week Per Patient				
arithmetic mean (standard deviation)	83.7 (± 25.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Adverse Events (AEs)

End point title	Number of Patients With Adverse Events (AEs)

End point description:

AEs were documented at each (scheduled or unscheduled) study visit. Severity and seriousness of all AEs were documented by the investigator according to pre-defined criteria. The SAF population included 58 patients who received at least one infusion of Human-c1 rhFVIII in the GENA-21b trial.

End point type	Secondary

End point timeframe:

At each study visit over the study duration (7–9 months)

End point values	SAF-Population			
Subject group type	Subject analysis set			
Number of subjects analysed	58			
Units: Patients				
AE	34			
No AE	24			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were reprorted throughout the study from screening visit until study completion visit. Planned surgeries were exempted from the SAE reporting requirement.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Safety Population (SAF)

Reporting group description:

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

Serious adverse events	Safety Population (SAF)		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 58 (6.90%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basosquamous carcinoma			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Safety Population (SAF)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 58 (58.62%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	18		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	2		
Lymphadenopathy			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	2		
General disorders and administration site conditions			

Pyrexia subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Gastritis subjects affected / exposed occurrences (all)	 3 / 58 (5.17%) 3 2 / 58 (3.45%) 3 2 / 58 (3.45%) 2		
Respiratory, thoracic and mediastinal disorders Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	 2 / 58 (3.45%) 2 3 / 58 (5.17%) 3		
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 2 / 58 (3.45%) 2 2 / 58 (3.45%) 2		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) Pain in extremity	 4 / 58 (6.90%) 9 2 / 58 (3.45%) 2 		

subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	3		
Infections and infestations			
Influenza			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	6		
Nasopharyngitis			
subjects affected / exposed	12 / 58 (20.69%)		
occurrences (all)	17		
Urinary tract infection			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2015	Amendment 02: • ABO Blood Type: Capture of information on ABO blood type was included in order to determine the association between the half-life of Human-cl rhFVIII with ABO blood type. • Hemophilia Joint Health Score (HJHS): assessed within 3 months preceding the screening visit was also acceptable as HJHS will not significantly change in the short term. Clarification regarding the version of HJHS to be used was included and corresponding reference was updated • Information on target joints was to be captured in order to better characterise the patient's bleeding history • SAE Reporting: Protocol was updated to exempt all planned surgeries from the SAE reporting requirement and not only surgeries planned before study start • for more clarity time windows for PK visit assessments were included.
26 October 2015	Amendment 03 . The following was included: • inhibitor testing at: Day 14, Day 30, End of Phase I, Phase II 2M and 4M visits; 3-8 weeks after surgery •stopping rules related to the development of a neutralizing antibody (inhibitor) to FVIII • time frame for a second confirmatory test in case an inhibitor result is positive The following was excluded: • participation of patients who are not qualified to give legal consent in Netherlands

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported