



## Clinical trial results:

**Prospective, open-label, multicentre phase 3b study to assess the efficacy and safety of individually tailored prophylaxis with Human-cl rhFVIII in previously treated adult patients with severe haemophilia A**

**Summary**

EudraCT number	2013-001556-35
Trial protocol	GB SK CZ HU BG AT ES DE PL
Global end of trial date	16 January 2015

### Results information

Result version number	v1 (current)
This version publication date	06 January 2017
First version publication date	06 January 2017

### Trial information

#### Trial identification

Sponsor protocol code	GENA-21
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01863758
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Octapharma AG
Sponsor organisation address	Seidenstraße 2, Lachen, Switzerland, CH-8853
Public contact	Johann Bichler, Octapharma AG, +41 55451 21 77, johann.bichler@octapharma.ch
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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	13 January 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 January 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial was to compare the annualized total bleeding rate of individually tailored prophylaxis with the historical bleeding rate observed in patients having received on-demand treatment with Human-cl rhFVIII from study GENA-01. Thereafter, patients were treated prophylactically every other day or 3x/week with a dose of 30–40 IU/kg body weight for about 1–3 months until PK data have been analysed and discussed with the investigator (Phase-I). Then, patients were treated prophylactically for 6 months (Phase-II) whereby the prophylactic dose and dosing interval were recommended for each patient based on the analysis of individual PK data obtained at the Initial PK visit. Specifically, it was calculated for how long a certain dose will provide FVIII:C plasma concentrations (one-stage assay) of  $\geq 0.01$  IU/mL.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and ICH-GCP, and national regulatory requirements. In- and exclusion criteria were carefully defined in order to protect subjects from contraindications, interactions with other medication and safety factors associated with the investigational medicinal product. Throughout the study safety was assessed, such as occurrence of adverse events, measurement of vital signs and physical examinations. In particular, patients were checked whether they had developed an inhibitor to factor VIII.

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	29 August 2013
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: 9
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Bulgaria: 31
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 4
Worldwide total number of subjects	66
EEA total number of subjects	66

Notes:

<b>Subjects enrolled per age group</b>	
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)	65
From 65 to 84 years	1
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment period August 2013 - June 2014

In total, 66 patients previously treated with Human-cl rhFVIII suffering from haemophilia A were enrolled in 20 study centers in Austria, Bulgaria, Germany, Hungary, Poland, Romania, Slovakia and United Kingdom.

### Pre-assignment

Screening details:

Severe haemophilia A (FVIII:C <1%), Male patients  $\geq 18$  years of age, previous treatment with a FVIII concentrate for at least 150 exposure days (EDs), Good documentation regarding dosing and bleeding frequency in the 6 months preceding study start, Immunocompetence (CD4+ count >200/ $\mu$ L), negative for HIV, freely given informed consent.

### Period 1

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

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	Initial PK Evaluation Phase

Arm description:

Duration: 72 hours

Arm type	Experimental
Investigational medicinal product name	Human-cl rhFVIII
Investigational medicinal product code	Nuwiq
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 60 +/- 5 IU/kg

<b>Arm title</b>	Prophylactic Treatment - Phase I
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Arm description:

Patients were to be treated prophylactically every other day or 3x/week with a dose of 30–40 IU/kg body weight (BW) for about 1–3 months until PK data have 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.

Arm type	Experimental
Investigational medicinal product name	Human-cl rhFVIII
Investigational medicinal product code	Nuwiq
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 30 - 40 IU/kg every other day or 3x/week

<b>Arm title</b>	Prophylactic Treatment - Phase II
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Arm description:

Patients were to be treated prophylactically for 6 months. The prophylactic dose and dosing interval were recommended for each patient based on the analysis of individual PK data obtained at the Initial

PK Visit. Specifically, it was calculated for how long a certain dose will provide FVIII:C plasma concentrations (one-stage assay) of  $\geq 0.01$  IU/mL using calculated elimination half-lives. The goal was to determine the maximum regular prophylactic dosing interval that can be achieved with a dose of not more than 60–80 IU/kg and that is capable of maintaining a trough level of  $\geq 0.01$  IU/mL.

Arm type	Experimental
Investigational medicinal product name	Human-cl rhFVIII
Investigational medicinal product code	Nuwiq
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose and dosing interval: individually PK tailored

<b>Number of subjects in period 1</b>	Initial PK Evaluation Phase	Prophylactic Treatment - Phase I	Prophylactic Treatment - Phase II
Started	66	66	66
Completed	66	66	65
Not completed	0	0	1
Lost to follow-up	-	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	66	66	
Age categorical			
Units: Subjects			
Adults (18-64 years)	65	65	
From 65-84 years	1	1	
Adolescents (12-17 years)	0	0	
From 65 to 84 years	0	0	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	66	66	

### Subject analysis sets

Subject analysis set title	PROPH analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients in the ITT population who entered the Prophylactic Treatment—Phase II of the study (i.e. had at least one prophylactic treatment in Phase II)

Subject analysis set title	PROPH-PP analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients in the PP population who entered the Prophylactic Treatment—Phase II of the study

- who had 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 had no significant dosing or treatment errors, e.g. several unexplained interruptions of individual prophylaxis with Human-cl rhFVIII, e.g. >20% of prophylactic infusions were not given within the prescribed treatment intervals ( $\pm 1$  day)

Reporting group values	PROPH analysis set	PROPH-PP analysis set	
Number of subjects	66	58	
Age categorical			
Units: Subjects			
Adults (18-64 years)	65	57	
From 65-84 years	1	1	
Adolescents (12-17 years)	0	0	
From 65 to 84 years	0	0	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	66	58	



## End points

### End points reporting groups

Reporting group title	Initial PK Evaluation Phase
Reporting group description:	
Duration: 72 hours	
Reporting group title	Prophylactic Treatment - Phase I
Reporting group description:	
Patients were to be treated prophylactically every other day or 3x/week with a dose of 30–40 IU/kg body weight (BW) for about 1–3 months until PK data have 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.	
Reporting group title	Prophylactic Treatment - Phase II
Reporting group description:	
Patients were to be treated prophylactically for 6 months. The prophylactic dose and dosing interval were recommended for each patient based on the analysis of individual PK data obtained at the Initial PK Visit. Specifically, it was calculated for how long a certain dose will provide FVIII:C plasma concentrations (one-stage assay) of $\geq 0.01$ IU/mL using calculated elimination half-lives. The goal was to determine the maximum regular prophylactic dosing interval that can be achieved with a dose of not more than 60–80 IU/kg and that is capable of maintaining a trough level of $\geq 0.01$ IU/mL.	
Subject analysis set title	PROPH analysis set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All patients in the ITT population who entered the Prophylactic Treatment—Phase II of the study (i.e. had at least one prophylactic treatment in Phase II)	
Subject analysis set title	PROPH-PP analysis set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All patients in the PP population who entered the Prophylactic Treatment—Phase II of the study – who had 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 had no significant dosing or treatment errors, e.g. several unexplained interruptions of individual prophylaxis with Human-cl rhFVIII, e.g. >20% of prophylactic infusions were not given within the prescribed treatment intervals ( $\pm 1$ day)	

### Primary: Comparison of Annualised Total Bleeding Rates (ABR)

End point title	Comparison of Annualised Total Bleeding Rates (ABR) <sup>[1]</sup>
End point description:	
The comparison of the annualized total bleeding rate of individually tailored prophylaxis with the historical bleeding rate observed in patients having received on-demand treatment with Human-cl rhFVIII from study GENA-01. Reduction of the annualized total bleeding rate observed in the GENA-01 study (58.1 total bleeding episodes per patient per year) by 50% during individually tailored prophylaxis.	
End point type	Primary
End point timeframe:	
from start of phase II to end of phase II	

#### 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 confirmative 1-sided 1-sample Poisson-test demonstrated that the mean annualised total bleeding rate (ABR) in patients with individually tailored prophylaxis (3.13) is at least 50% below the mean ABR rate in GENA-01 trial (49.36), with the upper bound of the mean ABR 95% CI 3.80) and 97.5% CI (3.90) both lower than 50% of the mean ABR in GENA-01 (24.68). Excluding 1 patient with numerous BEs despite prophylaxis before study entry and during Phase-II (ABR 96 & 107, respectively) ABR is 1.5.



<b>End point values</b>	PROPH analysis set	PROPH-PP analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	58		
Units: Annualised Total Bleeding Rates				
arithmetic mean (standard deviation)	3.05 ( $\pm$ 13.43)	1.05 ( $\pm$ 2.83)		

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AE were reported throughout the whole study. 24 hours SAE reporting requirement. Waiver from 24 hours SAE reporting: hospitalization for the treatment of a (disease-related) BE assessed as unrelated to IMP treatment.

Adverse event reporting additional description:

All SAEs, whether suspected to be related to study treatment or not, are reported by telephone, fax or e-mail immediately to the responsible Clinical Project Manager, study monitor, or to the responsible local CRO. AEs were evaluated at each patient visit.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

### Reporting groups

Reporting group title	Safety analysis population SAF
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Reporting group description:

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

Serious adverse events	Safety analysis population SAF		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 66 (7.58%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Tenotomy			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Haematemesis			

subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1.5 %

<b>Non-serious adverse events</b>	Safety analysis population SAF		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 66 (36.36%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign renal neoplasm			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Vascular disorders			
Bloody discharge			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Surgical and medical procedures			
Tenotomy			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		

General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	2		
Feeling cold			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Immune system disorders			
Atopy			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Splinter			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Lower limb fracture			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	5 / 66 (7.58%) 9		
Dizziness subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		
Blood and lymphatic system disorders Lymphadenitis subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)  Haematemesis subjects affected / exposed occurrences (all)  Toothache subjects affected / exposed occurrences (all)  Dyspepsia subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1  1 / 66 (1.52%) 1  2 / 66 (3.03%) 3  1 / 66 (1.52%) 1		
Skin and subcutaneous tissue disorders Psoriasis subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		
Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)  Arthropathy	4 / 66 (6.06%) 7		

subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	2		
Spinal pain			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Arthritis			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	5 / 66 (7.58%)		
occurrences (all)	6		
Peritonsillar abscess			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Postoperative wound infection			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	2		
Gastroenteritis viral			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 January 2014	<p>Amendment 02</p> <ul style="list-style-type: none"><li>• One of the objectives of the study was to assess the TGA in terms of its usefulness in individualising therapy for patients on prophylaxis. Unfortunately, the TGA samples from the PK assessment of 31 patients could not be analysed because samples thawed during transit to the laboratory. In order to end up with a reasonable number of patients for whom this parameter could be analysed it was decided to increase the number of patients from approximately 55 patients enrolled with the aim to have evaluable data on 50 patients, to 65 patients enrolled with the aim to have evaluable data on 60 patients.</li><li>• The efficacy analysis plan was supplemented with a secondary analysis regarding the analysis of the bleeding rate and treatment of bleeding episodes as requested by FDA for the completed GENA studies GENA-01, GENA-03 and GENA-08.</li><li>• The wording was modified to better explain the BLEED and BLEED-PP population i.e. that the populations were those of treated bleeds.</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported