# 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

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Primary Objective• To compare the annualised 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-01Secondary...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Coagulopathies and bleeding diatheses (excl thrombocytopenic) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON44091

**Source**
ToetsingOnline

**Brief title**
phase 3b study with Human-cl rhFVIII in patients with severe haemophilia A

### Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

**Synonym**
bleeding disease, Heamophilia

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Octapharma AG
**Source(s) of monetary or material Support:** Octapharma AG

## Intervention

**Keyword:** haemophilia A, Human-cl rhFVIII, Open-label, Phase 3b

## Outcome measures

### Primary outcome

Primary Endpoint

• Reduction of the annualised total bleeding rate observed in the GENA-01 study (58.1 total bleeding episodes per patient per year) by 50% during individually tailored prophylaxis

### Secondary outcome

Secondary Endpoints

1. Reduction of the annualised spontaneous bleeding rate observed in the GENA-01 study (38.5 spontaneous bleeding episodes per patient per year) by 50% during individually tailored prophylaxis

2. Reduction of the annualised bleeding rate observed in GENA-01 by 50% in patients with 2x/week prophylaxis or less

3. Median prophylactic dosing interval during individually tailored prophylaxis

4. Safety and tolerability of Human-cl rhFVIII by monitoring adverse events (AEs) throughout the study

Additional Endpoints

1. Descriptive efficacy of Human-cl rhFVIII in the treatment of breakthrough BEs

2. Descriptive efficacy of Human-cl rhFVIII in surgical prophylaxis

3. Correlation between VWF antigen concentration and half-life of Human-cl

rhFVIII

4. Association between ABO blood type and half-life of Human -cl rhFVIII

5. Human-cl rhFVIII consumption data (FVIII IU/kg per month per patient) during

individually tailored prophylaxis

# Study description

**Background summary**

Haemophilia A is an inherited sex-linked coagulation disorder in which affected males do not produce functional coagulation factor VIII (FVIII) in sufficient quantities to achieve satisfactory haemostasis, leading to bleeding diathesis. Most bleeding episodes occur in the patient*s joints and muscles. Without adequate treatment, repeated haemarthroses and haematoma lead to long-term sequelae with severe disability. Other bleeding sites, although less frequent but more severe, are the central nervous system, the urinary or gastrointestinal tract, the eyes, and the retroperitoneum. In addition, patients with haemophilia A are at high risk of developing major and life-threatening bleeding even after minor surgical interventions, such as tooth extractions. The optimal treatment of haemophilia A is replacement of FVIII using FVIII concentrate either obtained by fractionation of human plasma or manufactured by recombinant DNA technology. Human-cl rhFVIII is a recombinant human factor VIII concentrate developed by Octapharma. In contrast to other available recombinant FVIII concentrates in Europe, which are expressed in hamster cells, Human-cl rhFVIII is expressed in a human cell line.

Human-cl rhFVIII (brand name Nuwiq.® ) was approved in July 2014 by the European Medicine Agency (EMA) for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency) in all age groups. It has also been approved in Canada and Australia, and is currently being reviewed by Health Authorities of other countries (e.g. FDA). The current study serves to collect further data on Human-cl rhFVIII by evaluating the approach to individualize prophylactic treatment based on the patient*s individual PK assessment with Human-cl rhFVIII.

**Study objective**

Primary Objective
• To compare the annualised 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

Secondary Objectives
1. To compare the annualised spontaneous bleeding rate of individually tailored prophylaxis with the historical bleeding rate observed in patients having received on-demand treatment with Human-cl rhFVIII
2. To compare the annualised total bleeding rate in patients with 2x/week (or less) prophylaxis with the historical bleeding rate observed in patients having received on-demand treatment with Human-cl rhFVIII
3. To assess the median prophylactic dosing interval
4. To assess the PK of Human-cl rhFVIII in terms of FVIII:C
5. To assess the safety of Human-cl rhFVIII

Additional Objectives
1. To assess the clinical efficacy of Human-cl rhFVIII in the treatment of breakthrough bleeding episodes (BEs)
2. To assess the clinical efficacy of Human-cl rhFVIII in surgical prophylaxis
3. To assess the correlation of VWF antigen concentration and half-life of Human-cl rhFVIII
4. To assess the association between ABO blood type and half-life of Human-cl rhFVIII
5. To assess Human-cl rhFVIII consumption data ( exploratory)

**Study design**

This is a prospective, open-label, multicentre phase 3b study investigating the efficacy and safety of individually tailored prophylaxis with Human-cl rhFVIII in previously treated adult patients with severe haemophilia A.

The study consists of three (3) phases, i.e., the PK Evaluation Phase, the Prophylactic Treatment*Phase I, and the Prophylactic Treatment*Phase II.
• The PK Evaluation Phase will last for 72 hours (i.e., 3 days).
• The purpose of Prophylactic Treatment*Phase I, which will last for 1-3 months, is to treat the patients prophylactically every other day or 3x/week with a dose of 30-40 IU/kg BW until individual PK data have been analysed and discussed with the investigator .
• In Prophylactic Treatment*Phase II, patients will be treated prophylactically for 6 months. The recommended prophylactic doses and dosing intervals are determined 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 and after consultation with the investigator.

The study duration for each patient will be approximately 7-9 months, and the overall study duration will be about 2 years.

The study will be stopped if more than 3 patients develop a neutralizing antibody ( inhibitor) to Human-cl rhFVIII

## Intervention

Human-cl rhFVIII is a human cell line derived recombinant FVIII concentrate for intravenous use. Vials contain either 250, 500, 1000, or 2000 international units (IU) of freeze-dried FVIII concentrate, each to be reconstituted in 2.5 mL water for injections. Human-cl rhFVIII should be injected intravenously by bolus injection at a maximum rate of 4 mL/min. Continuous infusion is prohibited

Dosing of the IMP:
Initial PK Evaluation (72 hours):
60 ± 5 IU FVIII/kg, according to labelled potency

Prophylactic Treatment*Phase I (1-3 months):
Patients will 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 have been analysed and discussed with the investigator. Dose escalations are allowed in case of an inadequate frequency and severity of breakthrough bleeding episodes in accordance with the institution*s standard clinical care.

Prophylactic Treatment*Phase II (6 months):
Patients will be treated prophylactically for 6 months. The recommended prophylactic doses and dosing intervals are determined 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 and after consultation with the investigator.

Based on an appropriate PK model, various dosing intervals (usually 12-hour intervals) and corresponding doses (in IU/kg) will be 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 is to use the maximum regular prophylactic dosing interval that can be achieved with a maximum dose of preferably not more than 65 IU/kg and that maintains a trough level of >= 0.01 IU/mL.

## Study burden and risks

Partifipation in this study could take 7-9 months and could include up to 9 visits to the study centre. In between visits the patient also has telefonic contact with the site personnel
The following procedures will be done during the visits:
• 1x Check inclusion/exclusion criteria
• 1x Documentation of Medical History, as well as other medications the patient takes

• 4x Vital signs measurement
• 2x Height and body weight measurement
• 2x Physical examination including checking joints
• 8x Blood sampling
• 6x patient diary review
• 4x Documentation of side effects and changes in other medication

Infusion study medication, dosing and frequenxy on an individual basis

A general risk associated with all kinds of factor VIII concentrates (whether recombinant or produced from human blood) is the possible development of inhibiting antibodies ('inhibitors') against factor VIII. These are proteins that the body may make and which prevent the infused factor VIII from working properly. Inhibitors can reduce the effect of the factor VIII treatment.Clinical studies performed with Human-cl rhFVIII suggest that the risk of developing inhibitors to Human-cl rhFVIII is not higher than with other factor VIII concentrates.

In rare cases, as with other factor VIII concentrates, allergic reactions to Human-cl rhFVIII might occur. The symptoms might range from burning and stinging at the injection site, swellings, fever, chills, nausea, vomiting, flushing, rash, hives, headache, low blood pressure, feeling tired, restlessness, a faster heart rate, tingling and wheezing, to chest tightness and shortness of breath. In very rare cases, a severe allergic reaction might occur.

The following adverse drug reactions were observed in 135 patients (previously treated with factor VIII) who participated in clinical studies with Human-cl rh FVIII: paresthesia headache, vertigo, dry mouth, back pain, injection site inflammation, injection site pain, non-neutralising anti factor VIII antibody. All these adverse drug reactions occurred only once.

When blood is drawn, pain could be experienced, bruising at the site of injection, light-headedness, fainting, scarring, and on rare occasion infections.
When having blood pressure taken, the cuff may squeeze the arm and may cause irritation.

When having an IV (intravenous) injection, a needle that is attached to a tube and syringe containing the study drug will be inserted into a vein. Pain may be experienced, bruising, discoloration of the skin around the injection site, infection, and clotting.

There may also be other unknown risks, other than those listed above that we cannot predict. As for any new drug, extra care has to be taken to monitor possible unexpected medical problems or side effects.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

(a) Severe haemophilia A (FVIII:C < 1%) according to medical history
(b) Male patients >= 18 years of age
(c) Previous treatment with a FVIII concentrate (regular prophylaxis with good compliance or on-demand treatment) for at least 150 EDs
(d) Good documentation regarding dosing and bleeding frequency in the 6 months preceding study start
(e) Immunocompetence (CD4+ count > 200/µL)
(f) Freely given written informed consent

### Exclusion criteria

Any coagulation disorder other than haemophilia A
(b) Present or past FVIII inhibitor activity (>= 0.6 BU) according to medical history
(c) Severe liver or kidney disease (ALT and AST levels > 5 times of upper limit of normal, creatinine > 120 µmol/L)
(d) Treatment with any investigational medicinal product (IMP) except FVIII IMP within 14 days prior to the screening visit

## Study design

### Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Prevention |

### Recruitment

NL

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| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 19-09-2016 |
| Enrollment: | 3 |
| Type: | Actual |

### Medical products/devices used

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| Product type: | Medicine |
| Brand name: | Nuwiq |
| Generic name: | Human-cl rhFVIII |

## Ethics review

Approved WMO

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| Date: | 04-08-2015 |

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| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 10-11-2015 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 18-02-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 17-03-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 15-04-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 25-05-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 13-03-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 05-04-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2014-002986-30-NL |
| ClinicalTrials.gov | NCT02256917 |
| CCMO | NL53759.042.15 |