Title	**Prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of *Human-cl rhFVIII* (simoctocog alfa) in patients with haemophilia A treated in routine clinical practice**
Protocol number	GENA-99
Protocol version	05
Date of protocol	26 Sep 2017
Active substance	Coagulation FVIII
Medicinal product	*Human-cl rhFVIII* (simoctocog alfa) Commercial name: *Nuwiq*®
Indications	Treatment and prevention of bleeding episodes (also during and after surgery) in patients with haemophilia A
Research question and objectives	To collect additional clinical data and to ensure consistency in the long-term between the outcome from pre-authorisation clinical studies (in 135 previously treated paediatric and adult patients) and routine clinical practice. Besides aspects such as general product safety and efficacy, there will be a focus on immunogenicity, particularly on inhibitor development. The diagnosis of FVIII inhibitor will be based on clinical observations and confirmed by FVIII inhibitor testing in the laboratory.
Countries	Countries from across the EU and other countries where *Nuwiq*® is commercially available
Marketing authorisation holder	Octapharma AG Seidenstrasse 2 8853 Lachen Switzerland
Author	[redacted]

STUDY OUTLINE

Title of Study: Prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of *Human-cl rhFVIII* in patients with haemophilia A treated in routine clinical practice

Study Rationale: Data from pre-authorisation studies are insufficient to estimate all aspects of therapy with FVIII products, especially with respect to immunogenicity. Therefore, to estimate the likelihood of rare side effects, such as the occurrence of FVIII inhibitors, and to bridge between the outcome from clinical trials and long-term clinical use, the purpose of this study is to assess the long-term immunogenicity, safety, and efficacy of *Nuwiq*® in patients with haemophilia A treated in routine clinical practice. Specifically, the study is designed to meet the requirements for post-authorisation studies as outlined in the 'Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products' by the European Medicines Agency (EMA), EMA/CHMP/BPWP/144533/2009.

Study Objectives: In addition to general product safety and efficacy, the focus of this study will be on immunogenicity, particularly on inhibitor development (EMA/CHMP/BPWP/144533/2009). The objectives of this study are:

- To assess the long-term immunogenicity and safety of *Nuwiq*® in treating or preventing bleeding episodes (BEs) in patients with haemophilia A
- To assess the long-term efficacy of *Nuwiq*® in treating or preventing BEs in patients with haemophilia A

Study Design: Prospective, multinational, non-interventional post-authorisation study

Study Population

According to Guideline EMA/CHMP/BPWP/144533/2009, the number of patients typically needed in a post-authorisation study with FVIII to cover immunogenicity aspects is 200.

- The goal is to collect data on 200 previously treated male patients of any age with haemophilia (FVIII:C ≤ 2%).
- Of the 200 enrolled patients, at least 100 patients should have severe haemophilia A (FVIII:C < 1%).
- The age distribution of enrolled patients should be evenly balanced; thus, approx. 60 patients should be < 12 years of age; also, at least 10 patients should be aged between 14–18 years.
- Patients with severe haemophilia A after successful immune tolerance induction (ITI) can also be included; the proportion of ITI patients should not exceed 25% of the entire cohort.

Data on patients having participated in pre-authorisation studies with *Nuwiq*® and patients starting treatment with *Nuwiq*® in additional clinical Good Clinical Practice (GCP) studies may be combined with data from patients agreeing to participate in this non-interventional study to count towards the required 200 patients.

Eligibility Criteria

Inclusion Criteria

(a) Haemophilia A (FVIII:C ≤ 2%) based on medical history; at least 100 patients should have severe haemophilia A (FVIII:C < 1%)
(b) Male patients of any age
(c) Previous treatment with a FVIII concentrate for more than 150 exposure days (EDs)
(d) Availability of detailed documentation (patient diary) covering either the last 50 EDs or the last 2 years per patient to confirm treatment modality (i.e., prophylaxis, on-demand, recent surgery, or immune tolerance induction)
(e) Inhibitor negative (< 0.6 BU) at study entry as confirmed by a recovery test with previous FVIII product and inhibitor test in a central laboratory
(f) Immunocompetence (CD4+ count > 200/µL), HIV-negative, or having a viral load < 200 particles/µL or < 400,000 copies/mL
(g) Decision to prescribe *Nuwiq*® before enrolment into the study
(h) Written informed consent by the patient or the patient's parent or legal guardian

Exclusion Criteria

Patients treated with any investigational medicinal product (IMP) except FVIII IMP within 30 days prior to the Screening Visit or patients planning to undergo treatment with any IMP other than *Nuwiq*® are not eligible for enrolment into the study.

Outcome Parameters

Immunogenicity and Safety

The study objective of assessing the long-term immunogenicity and safety of *Nuwiq*® will be evaluated using the following outcome parameters:

- Incidence of FVIII inhibitors, with the diagnosis
  - based on clinical observations and
  - confirmed by FVIII inhibitor testing in the laboratory
- Incidence of adverse drug reactions (ADRs), including hypersensitivity reactions

Efficacy

The study objective of assessing the long-term efficacy of *Nuwiq*® will be evaluated using the following outcome parameters:

- **Prophylactic treatment**
  - Annualised rate of breakthrough bleeding episodes (BEs)
  - FVIII consumption data
    - Number of EDs
    - Number of infusions (needed to treat a breakthrough BE)
    - FVIII IU/kg per infusion, per BE, per month, per year
- **On-demand treatment of bleeding episodes**
  - Annualised rate of bleeding episodes (BEs)
  - FVIII consumption data
    - Number of EDs
    - Number of infusions needed to treat a BE
    - FVIII IU/kg per infusion, per BE, per month, per year
  - Assessment of the effectiveness of treatment at the end of a BE by the patient
- **Surgical prophylaxis**
  - Details of the surgical intervention
  - FVIII consumption data
  - Details on concomitantly administered products, including any blood or blood product transfusions or colloidal plasma substitutes (such as albumin, hydroxyl starch, dextran, and gelatine)
  - Estimated and actual perioperative and postoperative bleeding volumes
  - Overall assessment of the effectiveness of surgical prophylaxis by the treating physicians

Patient characteristics

- Age, sex, ethnic origin
- Medical history (including age at first treatment with FVIII)
- FVIII inhibitor history
- FVIII genotype
- Family history of haemophilia
- HIV status
- Comorbidities that may significantly impact on blood coagulation/immune reaction
- Previous medication(s) and FVIII treatment regimen(s)
- Concomitant medication(s) and current FVIII treatment regimen

Optional PK assessment

An optional PK assessment to determine prophylactic treatment regimen of a patient may be conducted at the discretion of the treating physician. The dose and dosing interval will be calculated in the frame of this non-interventional study either based on an individual PK with 6 - 10 time points or on a population-based PK using 1-3 time points (including the possibility to combine 1 to 2 time-points from different infusions of *Nuwiq*® at the dose patient is routinely treated with). The population-PK option uses WAPPS (wapps-hemo.org) to model collected FVIII activity data from the withdrawn time-points and to provide an estimation of the patient PK. WAPPS is developed and provided online by McMaster University (Hamilton, Ontario Canada). Patients will consent to participate in this optional assessment.

Optional Quality of Life assessment (SF-36 Health Survey)

Patient's health-related quality of life may be measured using SF-36 health survey. This assessment will be performed only in countries where it is not considered interventional. Patients will consent prior to receiving the questionnaire. SF-36 health survey will be done at screening, every 6 months after enrolment and at completion visit.

Duration of Treatment: Patients from pre-authorisation studies can be followed up to at least 100 EDs, newly enrolled patients have to be treated and followed for at least 100 EDs. The overall duration of this post-authorisation study will be approximately 4 years. The study will be completed once 200 patients have been treated and followed up for at least 100 EDs, provided that:

- Age distribution is balanced (approx. 60 patients < 12 years of age; at least 10 patients aged between 14–18 years)
- At least 100 patients have severe haemophilia A (FVIII:C <1%)
- The proportion of ITI patients does not exceed 25% of the entire cohort

Data Analysis: Descriptive statistics

Milestones:	
Start of data collection	Q1 2016
End of data collection	Q2 2019
Study progress report	2 years after marketing authorisation
Final study report	Q1 2020

PROTOCOL SIGNATURES

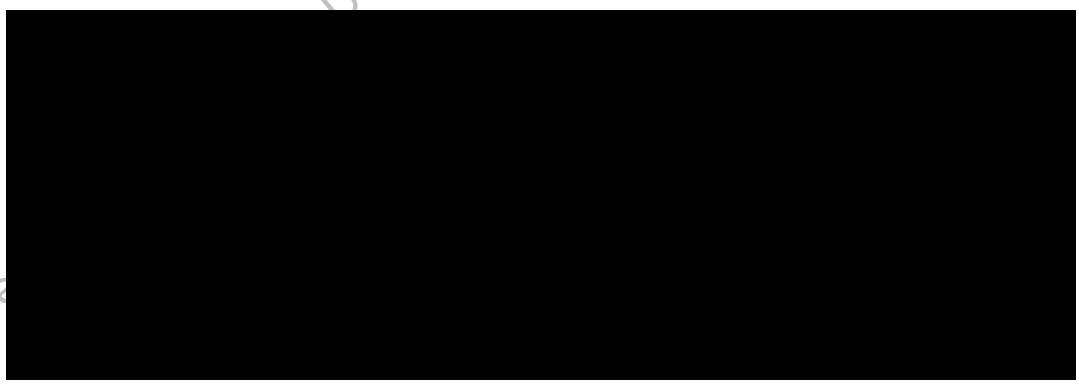
Signature of the Sponsor's Representative

This study is to be conducted in compliance with this protocol and applicable regulatory requirements.

[redacted]

Signature of the Author of the Protocol & Clinical Project Manager

This study is to be conducted in compliance with this protocol
and applicable regulatory requirements.



Signature of the Qualified Person Pharmacovigilance/Drug Safety Physician

This study is to be conducted in compliance with this protocol
and applicable regulatory requirements.

[redacted]

TABLE OF CONTENTS

APPENDIX

LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AUC	area under the curve
BE	bleeding episode
BU	Bethesda Unit
CI	confidence interval
CRF	Case Report Form
CRO	Contract Research Organisation
ED	exposure day
EMA	European Medicines Agency
FVIII	factor VIII
FVIII:C	FVIII coagulant activity
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
IEC	Independent Ethics Committee
IMP	investigational medicinal product
ITI	immune tolerance induction
IU	International Unit
PK	pharmacokinetics
PTP	previously treated patient
QoL	Quality of life
rFVIII	recombinant FVIII
rhFVIII	recombinant human factor VIII
SADR	serious adverse drug reaction
SAE	serious adverse event
SF-36	Short Form Health Survey
SOC	System Organ Class
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
VWF	von Willebrand factor
VWFAg	von Willebrand factor antigen
WFI	water for injections

1 MILESTONES

Milestone	Planned date
Start of data collection	Q1 2016
End of data collection	Q2 2019
Study progress report	2 years after marketing authorisation
Final study report	Q1 2020

2 RATIONALE AND BACKGROUND

2.1 Treatment of Haemophilia A

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. The transmission of viruses by plasma-derived coagulation factor concentrates in the 1970s and early 1980s sparked increased interest in producing FVIII products by recombinant DNA technology, and since the early 1990s, recombinant FVIII products have been commercially available [1].

Thus far, commercial unmodified recombinant FVIII (rFVIII) concentrates have been expressed in hamster cells. However, products derived from hamster cells may contain contaminants of non-human origin that may give rise to immune reactions. Also, the post-translational modifications of these proteins expressed in hamster cells are not identical to those of native human FVIII, potentially leading to immunogenic reactions and the development of inhibitors against rFVIII [2, 3].

Octapharma has developed *Nuwiq*® (simoctocog alfa), a fourth-generation recombinant human factor VIII (rhFVIII) concentrate for the control and prevention of bleeding episodes (BEs) and for surgical prophylaxis in patients with haemophilia A. In Europe, marketing authorisation for *Nuwiq*® was obtained through the centralised procedure on 22 July 2014..

2.2 Product Description

Nuwiq® is a B-domain deleted rhFVIII produced in human embryonic kidney cells (HEK 293F) [4]. *Nuwiq*® has been shown to be highly pure, with host-cell protein and DNA traces comparable to, or lower than, other marketed rFVIII products [5]. *Nuwiq*® has a high specific FVIII activity and characteristics similar to full-length rFVIII products. *Nuwiq*® displayed a higher binding capacity with von Willebrand factor (VWF) than comparator

products, thus minimizing circulating unbound FVIII and further reducing the potential risk of inhibitor development [5].

For rhFVIII, glycosylation and sulfation are vital for functionality and VWF binding affinity. *Nuwiq*® has been shown to be sulfated and glycosylated in ways comparable to human-plasma-derived FVIII. Most importantly, *Nuwiq*® is devoid of the antigenic Neu5Gc or alpha-Gal epitopes observed in Chinese Hamster Ovary- and Baby Hamster Kidney-derived rFVIII products. Both the avoidance of non-human glycan structures and the achievement of complete sulfation are proposed to lower the intrinsic immunogenicity of *Nuwiq*® compared with current rFVIII products [6].

For more detailed product information, refer to Section 6 and the Summary of Product Characteristics (SPC) of *Human-cl rhFVIII*.

2.2.1 Results from Clinical Studies for Market Authorisation

The clinical study program for market authorisation was developed with consideration of both EU and USA guidelines. Final results are available from 5 studies in a total of 135 previously treated patients. *Nuwiq*® was bioequivalent to the licensed full-length rFVIII Kogenate FS, with the ratio of the geometric means [90% CI] for AUC_{norm} (*Nuwiq*® relative to Kogenate FS) within the accepted range for bioequivalence of 0.8 to 1.25, and it was safe and efficacious in preventing and treating BEs. In particular, no inhibitor was detected, and no unexpected adverse event (AE) or related SAEs were reported in any of the studies.

2.2.2 Therapeutic Indications

Nuwiq® is indicated for the treatment and prophylaxis of bleeding in paediatric and adult patients with haemophilia A (congenital factor VIII deficiency).

2.2.3 Benefit-Risk Statement

Based on the available clinical evidence, *Nuwiq*® is safe and effective in the prevention and treatment of BEs and during surgical prophylaxis in patients with inherited FVIII deficiency.

Summary of safety profile

- Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have rarely been observed with FVIII preparations and may in some cases progress to severe anaphylaxis (including shock).
- Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. If such inhibitors occur, the condition will manifest as an insufficient clinical response. In such cases, the patient should contact the study site.

Tabulation of ADRs seen in the clinical development program of *Human-cl rhFVIII*

In clinical studies with *Nuwiq*® in previously treated paediatric (2 to 11 years, n = 58), adolescent (12 to 17 years, n = 3) and adult patients (n = 74) with severe haemophilia A, a total of 8 adverse drug reactions (ADRs) (6 in adults, 2 in children) were reported in 5 patients (3 adults, 2 children).

Table 1 is sorted by MedDRA System Organ Class (SOC) and Preferred Term (PT).

Table 1 Occurrence of adverse drug reactions (ADRs, n=8) in clinical studies with *Nuwiq*® in 135 previously treated patients with severe haemophilia A

MedDRA Standard System Organ Class	Adverse reaction (Preferred Term)	Frequency*
Nervous system disorders	Parasthesia Headache	Uncommon
General disorders and administration site conditions	Injection site inflammation Injection site pain	Uncommon
Investigations	Non-neutralising anti factor VIII antibody positive	Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Uncommon
Ear and labyrinth disorders	Vertigo	Uncommon
Gastrointestinal disorders	Dry mouth	Uncommon

* All ADRs occurred only once. With a total number of studied patients of 135, the frequency classification of an ADR occurring only once cannot be less than 'uncommon.'

Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Description of selected ADRs

One case of non-neutralizing anti-factor VIII antibody was detected in one adult patient (see Table 1). The sample was tested by the central laboratory at eight dilutions. The result was positive only at dilution factor 1, and the antibody titre was very low. Inhibitory activity, as measured by the modified Bethesda assay, was not detected in this patient. Clinical efficacy and in-vivo recovery of *Nuwiq*® was not affected in this patient.

Paediatric population

The frequency, type, and severity of ADRs in children are assumed to be the same as in adults.

2.3 Study Rationale

The number of patients enrolled in the pre-authorisation clinical studies with *Nuwiq*® was 135 (see Section 2.2.1), which is considered adequate to provide relevant information on general safety aspects and to demonstrate the efficacy of *Nuwiq*® in terms of its ability to restore factor VIII levels and stop or prevent bleeding. However, data from pre-authorisation studies are insufficient to estimate all aspects of therapy with FVIII products, especially with respect to immunogenicity (EMA/CHMP/BPWP/144533/2009).

Therefore, to estimate the likelihood of rare side effects, such as the occurrence of FVIII inhibitors, and to bridge between the outcome from clinical trials and long-term clinical use, the purpose of this study is to assess the long-term immunogenicity, safety, and efficacy of *Nuwiq*® in patients with haemophilia A treated in routine clinical practice.

Specifically, the study is designed to meet the requirements for post-authorisation studies as outlined in 'Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products' by the European Medicines Agency (EMA), EMA/CHMP/BPWP/144533/2009.

3 STUDY OBJECTIVES AND OUTCOME PARAMETERS

3.1 Study Objectives

The overall objective of this study is to collect clinical data in addition to those obtained during the clinical study program and to ensure the consistency, in the long-term, between the outcome from pre-authorisation clinical studies (in 135 previously treated paediatric and adult patients) and routine clinical practice.

In addition to general product safety and efficacy, the focus of this study will be on immunogenicity, particularly on inhibitor development (EMA/CHMP/BPWP/144533/2009).

The objectives of this study are:

- To **assess the long-term immunogenicity and safety** of *Nuwiq*® in treating or preventing bleeding episodes (BEs) in patients with haemophilia A
- To **assess the long-term efficacy** of *Nuwiq*® in treating or preventing BEs in patients with haemophilia A

The study will be performed in countries from across the EU and other countries where *Nuwiq*® is intended to be marketed.

3.2 Outcome Parameters

3.2.1 Outcome parameters for assessing the long-term immunogenicity and safety of Human-cl rhFVIII

The study objective of assessing the long-term immunogenicity and safety of *Nuwiq*® in treating or preventing BEs in patients with haemophilia A will be evaluated using the following outcome parameters:

- Incidence of FVIII inhibitors, with the diagnosis
  - based on clinical observations and
  - confirmed by FVIII inhibitor testing in the laboratory
- Incidence of adverse drug reactions (ADRs), including hypersensitivity reactions

3.2.2 Outcome parameters for assessing the long-term efficacy of Human-cl rhFVIII

The study objective of assessing the long-term efficacy of *Nuwiq*® in treating or preventing BEs in patients with haemophilia A will be evaluated using the following outcome parameters:

- **Prophylactic treatment**
  - Annualised rate of breakthrough BEs
  - FVIII consumption data
    - Number of EDs
    - Number of infusions (needed to treat a breakthrough BE)
    - FVIII IU/kg per infusion, per BE, per month, per year
- **On-demand treatment of bleeding episodes**
  - Annualised rate of BEs
  - FVIII consumption data
    - Number of EDs
    - Number of infusions needed to treat a BE
    - FVIII IU/kg per infusion, per BE, per month, per year
  - Assessment of the effectiveness of treatment at the end of a BE by the patient (see Section 8.1.2)
- **Surgical prophylaxis**
  - Details of the surgical intervention (see Section 8.1.3)
  - FVIII consumption data (see Section 8.1.3)
  - Details on concomitantly administered products, including any blood or blood product transfusions or colloidal plasma substitutes (such as albumin, hydroxyl starch, dextran, or gelatine)
  - Estimated and actual perioperative and postoperative bleeding volumes
  - Overall assessment of the effectiveness of surgical prophylaxis by the treating physicians (see Section 8.1.3)
- **Optional PK Analysis**
  - FVIII consumption data following PK-based changes in prophylaxis regimen (see Section 8.3)
  - Annualised rate of BEs following PK-based changes in prophylaxis regimen
- **Optional quality of life (QoL) assessment**
  - Health-related QoL(SF-36) in haemophilia A patients using *Nuwiq*®
  - Health-related QoL (SF-36) following PK-based changes in prophylaxis regimen

3.2.3 Patient characteristics

For patient characteristics to be recorded, refer to Section 7.2.1.

4 STUDY DESIGN

This is a prospective, multinational, non-interventional post-authorisation study designed to assess the long-term immunogenicity, safety, and efficacy of *Nuwiq*® in patients with haemophilia A treated in routine clinical practice.

The study design complies with Guideline EMA/CHMP/BPWP/144533/2009. In brief, 200 male patients of any age with haemophilia (FVIII:C ≤ 2%) will be treated and followed for at least 100 EDs. Of the 200 enrolled patients, at least 100 patients should have severe haemophilia A (FVIII:C < 1%). The overall duration of this study will be approximately 4 years. The testing schedule for FVIII inhibitors as predefined in Guideline EMA/CHMP/BPWP/144533/2009 is given in Table 3.

5 STUDY POPULATION

According to Guideline EMA/CHMP/BPWP/144533/2009, the number of patients typically needed in a post-authorisation study with FVIII to cover immunogenicity aspects is 200. In a cohort of 200 patients and assuming an inhibitor incidence of 1.5% or higher, there is at least 95% probability to observe antibodies in one or more patients.

An EMA expert meeting on FVIII products and inhibitor development agreed that the risk of inhibitor formation related to an individual product should be evaluated in previously treated patients (PTPs), because patients with a high degree of previous exposure should be immunotolerant to FVIII and are considered to be a better suited study population (EMA/CHMP/BPWP/144533/2009).

- Therefore, the goal is to collect data on **200 previously treated male patients** of any age with haemophilia (FVIII:C ≤ 2%). Data from patients having participated in pre-authorisation studies with *Nuwiq*® and data from patients starting treatment with *Nuwiq*® in additional clinical Good Clinical Practice (GCP) studies may be combined with data from patients agreeing to participate in this non-interventional study to count towards the required 200 patients (see Section 7.5.2). **Patients from pre-authorisation studies** can be followed up to at least 100 EDs. **Newly enrolled patients** have to be treated and followed for at least 100 EDs.
- Of the 200 enrolled patients, at least 100 patients should have **severe haemophilia A** (FVIII:C < 1%).
- Because the results of a clinical study in children was evaluated as part of the marketing authorisation procedure, patients of every age group are eligible to be included in this study. The age distribution of enrolled patients should be evenly

balanced. Thus, of the 200 enrolled patients, approx. 60 patients should be **< 12 years of age**. Also, at least 10 patients should be aged between **14–18 years**.

- Patients with severe haemophilia A after successful immune tolerance induction (ITI) can also be included; the proportion of these **ITI patients** should not exceed 25% of the entire cohort.

5.1 Inclusion Criteria

Patients who meet all of the following criteria are eligible for the study:

(a) Haemophilia A (FVIII:C ≤ 2%) based on medical history; at least 100 patients should have severe haemophilia A (FVIII:C < 1%)
(b) Male patients of any age
(c) Previous treatment with a FVIII concentrate for more than 150 EDs
(d) Availability of detailed documentation (patient diary, log book, etc.) covering either the last 50 EDs or the last 2 years per patient to confirm treatment modality (i.e., prophylaxis, on-demand, recent surgery, or immune tolerance induction)
(e) Inhibitor negative (< 0.6 BU) at study entry as confirmed by a recovery test with previous FVIII product and inhibitor test in a central laboratory
(f) Immunocompetence (CD4+ count > 200/µL), HIV-negative, or having a viral load < 200 particles/µL or < 400,000 copies/mL
(g) Decision to prescribe *Nuwiq*® before enrolment into the study
(h) Written informed consent by the patient or the patient's parent or legal guardian

5.2 Exclusion Criteria

Patients treated with any investigational medicinal product (IMP) except FVIII IMP within 30 days prior to the Screening Visit or patients planning to undergo treatment with any IMP other than *Nuwiq*® are not eligible for enrolment into the study.

5.3 Withdrawal of Patients

Patients have the right to withdraw from the study at any time for any reason without the need to justify their decision. The treating physician also has the right to withdraw patients in case of ADRs or for other reasons.

In case of any withdrawal after study entry, the treating physician will make every possible effort to collect any required data and document the reason(s) for withdrawal in the CRF. If the reason for withdrawal of a patient is an ADR, the main specific event or laboratory test will be recorded in the CRF, and the treating physician will make every possible effort to clearly document the outcome.

6 MEDICINAL PRODUCT

6.1 Characterisation of Medicinal Product

Nuwiq® is formulated as a powder and solvent for solution for injection. Each vial of *Nuwiq*® contains either 250, 500, 1000, 2000, 2500, 3000 and 4000international units (IU) of freeze-dried simoctocog alfa concentrate, each to be reconstituted in 2.5 mL of sterilised water for injections (WFI). Complete product information is given in the SPC of *Nuwiq*®.

6.2 Packaging

In this non-interventional study, commercially available *Nuwiq*® will be used.

Nuwiq® is filled and lyophilised in glass vials. The solvent for reconstitution of the drug product, 2.5 mL sterilised WFI, is provided in prefilled syringes.

Each drug product vial is provided with a kit containing:

- One sterile vial adapter for reconstitution
- One butterfly needle
- Two alcohol swabs

Only the provided injection sets should be used because treatment failure can occur as a consequence of human coagulation factor VIII adsorption to the internal surfaces of some injection equipment.

6.3 Conditions for Storage and Use

Nuwiq® has a shelf life of 24 months at 2°C to 8°C. For further details on specific storage conditions, please refer to your country specific package insert. After reconstitution, chemical and physical in-use stability has been demonstrated for 24 hours when stored at room temperature. From a microbiological point of view, the product should be used immediately or within 3 hours after reconstitution. Keep the reconstituted solution at room temperature. Do not refrigerate after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

The powder should only be reconstituted with the supplied solvent (2.5 mL water for injections) using the supplied injection set. The vial should be gently rotated until all powder is dissolved. After reconstitution, the solution should be drawn back into the syringe.

Reconstituted medicinal product should be visually inspected for particulate matter and discoloration prior to administration. The reconstituted medicinal product is a clear,

colourless solution, free from foreign particles and has a pH of 6.5 to 7.5. Do not use solutions that are cloudy or have deposits.

6.4 Method of Administration

Nuwiq® should be administered by intravenous bolus injection. The infusion rate should not exceed 4 mL per minute.

The reconstituted solution should be used immediately or within 3 hours after reconstitution. Also, the reconstituted solution should be kept at room temperature.

The solution is normally clear or slightly opalescent and colourless. Solutions which are cloudy or have deposits must not be used. For further details please refer to your country specific package insert.

6.5 Treatment Regimen, Dose, and Dosing Interval

The treatment regimen (i.e., prophylactic treatment, on-demand treatment, ITI, or surgical prophylaxis) as well as the doses, dosing intervals, or dose adjustments will be determined at the discretion of the treating physician and should be recorded in the CRF. If deemed appropriate by the treating physician for the respective patient, options for individual adjustment of the prophylaxis regimen may be calculated from the results of a PK assessment.

Prophylactic treatment

For long-term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary. For further details please refer to your country specific package insert.

On-demand treatment of bleeding episodes

The following table can be used to guide dosing in bleeding episodes. For further details please refer to your country specific package insert.

Degree of haemorrhage	Factor VIII level required (%) (IU/dL)	Frequency of doses (hours) and duration of therapy (days)
Early haemarthrosis, muscle bleeding, or oral bleeding	20–40	Repeat every 12–24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.

Degree of haemorrhage	Factor VIII level required (%) (IU/dL)	Frequency of doses (hours) and duration of therapy (days)
More extensive haemarthrosis, muscle bleeding, or haematoma	30–60	Repeat infusion every 12–24 hours for 3 to 4 days or more until pain and acute disability are resolved.
Life threatening haemorrhages	60–100	Repeat infusion every 8 to 24 hours until threat is resolved.

Surgical prophylaxis

The following table can be used to guide dosing in surgery. For further details please refer to your country specific package insert.

Type of surgical procedure	Factor VIII level required (%) (IU/dL)	Frequency of doses (hours) and duration of therapy (days)
Minor surgery including tooth extraction	30–60	Every 24 hours, at least 1 day, until healing is achieved.
Major surgery	80–100 (pre- and postoperative)	Repeat infusion every 8–24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL).

Optional individual PK evaluation

The recommended dose for individual PK-injection is 60±5 IU/kg.

The dose for population PK *Nuwiq*® is the dose the patient is routinely treated (or actual prophylaxis infusion).

6.6 Concomitant Therapy

Concomitant therapies are at the discretion of the treating physician.

Patients should be asked to keep their treating physicians informed of any concomitant medications, FVIII products other than *Nuwiq*® (including the reason for using an alternative FVIII product), and significant non-drug therapies (including physical therapy and blood transfusions) they may be receiving and/or to record them in their treatment diaries (see Section 7.4). Any concomitant therapies will be recorded in the CRF.

In patients undergoing surgical prophylaxis, details on concomitantly administered products, including any blood or blood product transfusions or colloidal plasma substitutes (such as albumin, hydroxyl starch, dextran, or gelatine) will be documented.

6.7 Treatment Compliance

There will not be any specific procedures to monitor the patients' compliance with treatment. Compliance will be monitored by the treating physician as part of routine clinical practice and supported by the information in the treatment diary (see Section 7.4).

The treating physician should promote compliance by instructing the patient (or the patient's parent or legal guardian) to administer *Nuwiq*® exactly as prescribed and by emphasising that compliance is necessary for the patient's safety. The patient should be asked to contact his treating physician if he is unable, for any reason, to administer *Nuwiq*® as prescribed.

7 STUDY CONDUCT

Patient eligibility for enrolment into the study will be determined at the Screening Visit, during which demographic and baseline data will be recorded (Table 2).

Before patient inclusion, there should be no clinical suspicion of FVIII inhibitors, and a recovery and inhibitor test in a central laboratory is recommended to confirm that the patient is negative at study entry. An inhibitor test which is not negative should be confirmed by testing a second separately drawn sample in central laboratory. The recommended testing schedule for FVIII inhibitors is predefined in Guideline EMA/CHMP/BPWP/144533/2009 and is presented in Table 3.

An optional PK assessment to determine individualized or population based prophylactic treatment regimen of a patient may be conducted at the discretion of the treating physician. The dose and dosing interval will be calculated in the frame of this non-interventional study either based on an individual PK with 6 - 10 time points or a population PK with 1- 3 time points – (see Section 8.3 and Table 5).

Treatment regimen of a patient may be conducted at the discretion of the treating physician. The individual dose and dosing interval will be calculated in the frame of this non-interventional study.

Patient diaries will be evaluated for the total number of exposures per year and the mean dose per kg per patient/year (consumption). The intended treatment regimen for every patient at study entry and the reason for each ED will also be documented.

In case of bleeding, the particulars of the event will be documented, along with drug consumption data and the severity and treatment outcome assessed by both the clinician and the patient.

In case of surgery, details of the intervention will be collected, such as type of surgery (planned or emergency), mode of administration, drug consumption, and any complications that may occur.

Any adverse drug reactions (ADRs) will also be monitored.

The frequency of clinical and laboratory monitoring throughout the study will be at the discretion of the treating physician based on clinical requirements. Therefore, study visits will generally coincide with routine follow-up visits or with any emergency visits that may become necessary. The data that should be recorded at each Follow-up Visit until study completion are summarized in Table 2.

7.1 Flow Charts of Assessments

The flow chart of recommended assessments is given in Table 2, and the flow chart of inhibitor testing as recommended by Guideline EMA/CHMP/BPWP/144533/2009 is given in Table 3.

Table 2 Flow Chart of Assessments

Data to be recorded	Screening Visit	Follow-up and Study Completion Visits
Informed consent	X	
Eligibility criteria* (see also Table 3)	X	
Demographics	X	
Medical history	X	
Bleeding history in the previous 6 months	X	
FVIII inhibitor history	X	
FVIII genotype	X	
Family history of haemophilia (including FVIII inhibitor history)	X	
Body weight	X	
Body height	X	
Immunocompetence and viral status*	X	
Comorbidities[2]	X	X
Previous medication(s)	X	
Concomitant medication(s)	X	X
Previous FVIII treatment regimen(s)	X	
Current FVIII treatment regimen	X	X
Completion of SF-36†	X	X‡
Documentation of occupational physical demand	X	
PK analysis §	Any time during the study (Table 5)	
Bleeding episode data	throughout the study	
Surgery data	throughout the study	
Monitoring of SADRs and ADRs	throughout the study	
FVIII inhibitor status	see Table 3	

* Patients must be immunocompetent (CD4 lymphocytes >200/µL), HIV-negative, or have a viral load < 200 particles/µL or < 400 000 copies/mL).

† For patients 14 years of age and older who have consented for the optional assessment

‡ At follow up visits every 6 months after screening and completion visit

§ Optional, if deemed beneficial by treating physician and after patient's consent

The data that should be recorded during each patient visit are summarised in Section 7.2.

Table 3 Flow Chart of Inhibitor Testing as Recommended by Guideline EMA/CHMP/BPWP/144533/2009

Assessments	Previous FVIII product[2]	*Human-cl rhFVIII*[5]			
		ED 1	ED 10–15	ED 50–75	ED ~100
Inhibitor[1]	x[3]	x[4]	x	x	x
Recovery	x[3]	x	x	x	x

[1] After washout period; storage of backup sample is recommended.
Inhibitor tests should be performed when the plasma factor VIII level has reached a pre-substitution nadir (documentation for the last infusion should be provided).
Inhibitor re-testing using a second separately drawn sample as confirmatory measurement should be performed in the central laboratory.

[2] New patients, i.e., patients not recruited for pre-authorisation studies

[3] According to Guideline EMA/CHMP/BPWP/144533/2009, there should not be any clinical suspicion of inhibitors before inclusion into the study, and a recovery and inhibitor test in a central laboratory should confirm that the patient is inhibitor-negative at study entry.

[4] Baseline inhibitor testing before infusion of *Nuwiq*® at a central laboratory

[5] In addition to the tests specified in the table, testing should be carried out if there is any suspicion of inhibitors.

Details on the laboratory testing for FVIII inhibitors are given in Section 8.3.2.

7.2 Data Recorded During Each Visit

7.2.1 Screening Visit

The following data will be recorded:

- Informed consent
- Eligibility criteria
- Demographic data
  - Age
  - Ethnic origin
- Medical history (including age at first treatment with FVIII)
- Bleeding history in the previous 6 months (frequency of BEs)
- FVIII inhibitor history
- FVIII genotype
- Family history of haemophilia (including FVIII inhibitor history)
- Body weight
- Body height
- Immunocompetence (CD4+ count > 200/µL), HIV negative, or having a viral load < 200 particles/µL or < 400,000 copies/mL
- Viral status

- Comorbidities that may significantly impact on blood coagulation or immune reaction
- Previous medication(s)
- Concomitant medication(s)
- Previous FVIII treatment regimen(s) based on treatment diary covering either the last 50 EDs or the last 2 years per patient to confirm treatment modality (e.g., prophylaxis, on-demand, recent surgery, immune tolerance induction)
  - Doses and dosing frequency
  - Name of previous FVIII product(s)
- Current FVIII treatment regimen (e.g., prophylaxis on-demand)
  - Doses and dosing frequency
  - Name of current FVIII product
- Completion of Short Form Health Survey (SF-36): as the study is non-interventional completion of this form is optional and only patients who consent to participate in this assessment will be asked to complete this form.
- Documentation of occupational physical demand

Eligible patients agreeing to enter the study will receive and be asked to fill in a **treatment diary** (see Section 7.4).

7.2.2 Follow-up Visits and Study Completion Visit

Follow-up visits will be performed at the discretion of the treating physician (e.g., every 2–4 months) and/or at the time points specified in Table 3.

The following data will be documented:

- Current FVIII treatment regimen (e.g., prophylaxis, on-demand)
  - Doses and dosing frequency
- In case of bleeding episodes, see Section 8.1.2
- In case of surgery, see Section 8.1.3
- Concomitant medication(s)
- Monitoring of SADRs and ADRs
- FVIII inhibitor status
- SF-36 (optional) every 6 months after screening and at completion visit

7.2.3 Optional PK assessment for individual prophylaxis regimen

An optional PK analysis to determine individual prophylaxis regimen for a patient is offered in this non-interventional study. FVIII plasma level measurements will be performed at the discretion of the treating physician and if patient has given consent. FVIII:C levels measured after infusion of *Nuwiq*® up to 6 months prior to enrolment in the study are acceptable to perform the PK analysis, if no significant changes in patient's health or weight have been recorded .The dose and dosing interval will be calculated in the frame

of this non-interventional study either based on an individual PK with 6 - 10 time points or on a population-based PK using 1-3 time points (including the possibility to combine 1 to 2 time-points from different infusions of *Nuwiq*® at the dose the patient is routinely treated with). The population-PK option uses WAPPS (wapps-hemo.org) to model collected FVIII activity data from the withdrawn time-points and to provide an estimation of the patient PK. WAPPS is developed and provided online by McMaster University (Hamilton, Ontario Canada) [7].

7.3 Patient Codes

Each patient enrolled into this non-interventional study will be uniquely identifiable by a patient code consisting of the study code, centre code, and patient number. The centre code is assigned to the study site by Octapharma. At each site, enrolled patients will be numbered consecutively. Once assigned to a patient, a patient number will not be reused.

7.4 Treatment Diaries

Documenting treatment and bleeding data is an integral part of home treatment for haemophilia. In this study, patients will be provided with a treatment diary during the Screening Visit after inclusion into the study. Patients will be asked to complete their treatment diaries and to bring them along for review to each Follow-up Visit.

The following data can be recorded in the treatment diary:

- Infusion-related data: date and time of administration, dose, batch number, reason for infusion (i.e., prophylaxis, BE treatment).
- For BE data that can be documented (including patient assessment of treatment efficacy), see Section 8.1.1.
- Concomitant medications
- Adverse drug reactions (ADRs), including hypersensitivity reactions

During or after each follow-up visit, the information recorded in the patient diaries will be transcribed to the CRFs. The patient diaries are considered source data, and the originals will be included in the patient's medical record.

7.5 Study Duration

7.5.1 Planned Duration of the Study

The overall duration of this post-authorisation study will be approximately 4 years.

The study will be considered completed once 200 patients have been treated and followed for at least 100 EDs (see Section 5), provided that

- Age distribution is balanced (approx. 60 patients < 12 years of age; at least 10 patients aged between 14–18 years)
- At least 100 patients have severe haemophilia A (FVIII:C <1%)
- The proportion of ITI patients does not exceed 25% of the entire cohort

Also, all CRFs must have been completed and submitted to the Sponsor.

7.5.2 Planned Duration by Patient

Patients from pre-authorisation studies as well as patients from other interventional Phase III studies with *Nuwiq*® can be followed until they have completed at least 100 EDs. Patients enrolled into this non-interventional study will be treated and followed for at least 100 EDs.

7.6 Optional Quality of Life assessment (SF-36 Health Survey)

An optional quality of life assessment is offered in this non-interventional study. Hence, this assessment will be performed only in countries where it is not considered interventional. Patients need to additionally consent in order to receive the questionnaire. SF-36 health survey is a set of generic, coherent, and easily administered quality-of-life measures which relies upon patient self-reporting for routine monitoring and assessment of care outcomes in patients.

SF-36 will be completed by patients 14 years of age or older at screening, every 6 months after enrolment in the study and at completion visit who have consented to participate in this optional assessment.

8 ASSESSMENTS AND METHODS

A complete list of data recorded throughout the study is given in Section 7.2. This section provides details on individual data recorded as well as on assessment methods used.

8.1 Effectiveness Assessments

8.1.1 Prophylactic Treatment

FVIII consumption data to be documented

- Dates and times the IMP was infused
- IMP dose(s) and batch number(s)

8.1.2 Bleeding Episodes (BEs)

BE data to be documented in the treatment diary

For any BE occurring during the study, the following data should be recorded:

- BE type (spontaneous, traumatic, postoperative, other)
- BE site
- BE severity (minor, moderate, major)
- Date and time the BE first occurred or was first noticed
- Date and time the BE ended

FVIII consumption data to be documented

- Dates and times the IMP was infused
- IMP dose(s) and batch number(s)

Assessment of the efficacy of treatment at the end of a BE

At the end of a BE, treatment efficacy will be assessed either by the patient (or the patient's parent or legal guardian) or by the treating physician in case of on-site treatment using a scale including the four items 'excellent,' 'good,' moderate,' and 'none.' Based on this efficacy assessment, all efficacy ratings assessed as either 'excellent' or 'good' will be considered 'successfully treated.'

8.1.3 Surgical Prophylaxis

For any surgical procedure performed during the study, the following data should be recorded:

- Type of surgery (planned or emergency)
- Location of surgery
- Severity of surgery (minor, major); see item (a) below
- Details on dose(s) of *Nuwiq*® given pre-, intra-, or postoperatively; see item (b) below
- Pre-, intra-, and postoperative FVIII plasma levels, if routinely done; see item (c) below
- Estimated and actual perioperative and postoperative bleeding volumes
- Overall efficacy assessment at the end of surgical prophylaxis by the surgeon and the haematologist; see item (d) below
- Details on concomitantly administered products, including any blood or blood product transfusions or colloidal plasma substitutes (such as albumin, hydroxyl starch, dextran, and gelatine), but excluding drugs given for routine anaesthesia
- Monitoring of ADRs

Definitions of periods and time points before, during, and after surgery:

- **Preoperative** is defined as the time period of up to 3 hours before the start of surgery.
- The **end of surgery** is defined as the time immediately after the last surgical suture.
- **Postoperative** is the period from the end of surgery to the time the patient returns to his regular FVIII treatment regimen.
- The **end of the postoperative period** is the time the patient returns to his regular FVIII treatment regimen.

(a) Severity of surgery

Surgeries are defined as **major** if any of the following criteria are met:

- General or spinal/epidural anaesthesia required
- Opening into the great body cavities required
- Severe haemorrhage during surgery possible
- Haemostatic therapy for at least 6 days required
- Orthopaedic interventions involving joints (ankle, knee, hip, wrist, elbow, shoulder)
- 3rd molar extraction or extraction of ≥ 3 teeth
- Surgeries/conditions in which the patient's life is at stake

The classification is made prospectively. All other surgeries are classified as **minor**.

(b) Pre-, intra-, and postoperative doses of *Nuwiq*®

Details on the pre-, intra-, and postoperative administration of *Nuwiq*® will be recorded in the CRF and include the dates and times of administration as well as the batch numbers.

(c) FVIII plasma levels

If pre-, intra-, and postoperative FVIII plasma levels are routinely assessed at a given centre, they should also be recorded in the CRF, detailing when they were assessed (i.e., pre-, intra-, and/or postoperatively). The following time points for the determination of FVIII plasma levels are recommended:

- Immediately (≤ 30 min) before and 30 ± 15 min after preoperative infusion of *Nuwiq*®
- Immediately (≤ 30 min) before and 30 ± 15 min after each intraoperative bolus dose, if any
- Immediately (≤ 30 min) before and 30 ± 15 min after each postoperative dose, if any

(d) Assessment of the efficacy of surgical prophylaxis

At the end of the postoperative period, an overall assessment of the efficacy of treatment in the pre-, peri-, and postoperative periods using the 'excellent,' 'good,' moderate,' and 'none' scale will be done jointly by the surgeon and the haematologist. Based on this overall efficacy assessment, all efficacy ratings assessed as either 'excellent' or 'good' will be considered 'successfully treated.'

Table 4 Flow Chart of Assessments Performed for Surgical Interventions During the Study Period

	Any time before surgery	Within 3 hours before start	Intra-operatively	End[a]	POP day 1	Any POP day	At the end of POP period[b]
Type of surgery	x						
Location of surgery	x						
Severity of surgery	x						
Administration of *Human-cl rhFVIII*		x	(x)	(x)	(x)	(x)	(x)
FVIII plasma levels		#	(#)	(#)	(#)	(#)	(#)
Estimated bleeding volumes	x				x		
Overall efficacy assessment							SH
Concomitant medications	throughout observation period						
ADR monitoring	throughout observation period						

POP, postoperative; ( ) optional; # samples should be taken before (≤ 30 min) and 30 ± 15 min after *Nuwiq*® administration

[a] time immediately after the last surgical suture

[b] time the patient returns to his regular FVIII treatment regimen

SH, performed by surgeon and haematologist

8.2 Safety Assessments

To allow continuous monitoring of the product safety, all adverse drug reactions (ADRs) and other safety information as defined below have to be documented and reported to Octapharma.

8.2.1 Definition of (serious) adverse drug reaction and other safety information

Adverse drug reaction (ADR)

An **ADR** is a response to a medicinal product which is noxious and unintended [Directive 2001/83/EC Art 1(11)].

'Response' in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (see Annex IV, ICH-E2A Guideline).

ADRs may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure [Directive 2001/83/EC Art 101(1)]. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse drug reaction (SADR)

SADRs are ADRs that fulfil at least one of the following criteria:

- results in death
- is life-threatening (this implies that the patient was at risk of death at the time of the event; it does not refer to a reaction that hypothetically might have caused death if more severe)
- requires in-patient hospitalisation or prolongation of existing in-patient hospitalisation (hospitalisation does not refer to the treatment of an ADR on an out-patient status)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is a medically important event, e.g.,
  - suspected transmission via a medicinal product of an infectious agent,
  - inhibitor development,
  - thromboembolic events, or
  - other reactions that should be reported in an expedited manner although they did not immediately result in one of the above seriousness criteria, e.g., intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

8.2.2 Other relevant drug safety information

Any safety information relating to

- drug abuse (persistent, sporadic or intentional excessive use of a medicinal product inconsistent with the SPC or acceptable medical practice),
- misuse (situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information)
- overdose (administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.),
- medication errors (prescribing or dispensing error),
- interactions with other medicinal products or devices
- occupational exposure (an exposure to a medicinal product as a result of one's professional or non-professional occupation) associated with *Human-cl rhFVIII*, even if no ADR occurred.

8.2.3 Specifically monitored ADRs

ADRs of particular interest, i.e., hypersensitivity reactions and FVIII inhibitor development (see Section 2.2.3) as well as thromboembolic events, will be specifically monitored throughout the study using specific CRF pages.

Hypersensitivity reactions

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. *Nuwiq*® contains traces of human host cell proteins other than factor VIII. Early signs of hypersensitivity reactions include hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. A sample CRF for hypersensitivity reactions is provided in the Appendix 1: Case Safety Report Form, Case Safety Report Form - Annex 1: FVIII Inhibitor Development.

FVIII inhibitors

The diagnosis of factor VIII inhibitor will be based on clinical observations and be confirmed by factor VIII inhibitor testing in the central laboratory. The recommended laboratory testing schedule is given in Table 3. Items to be recorded include details on when blood samples were obtained for inhibitor testing and recovery tests (including dose), results of these tests and assay methodology, description of clinical symptoms suggesting inhibitor development, e.g. ineffective prophylaxis, need to increase dose and/or decrease prophylactic treatment interval, need to increase dose and/or number of infusions to treat a bleed. A sample CRF for FVIII inhibitor testing is provided in the Appendix 1: Case Safety Report Form, Case Safety Report Form - Annex 2: Hypersensitivity/Anaphylactic Reactions.

The occurrence of FVIII inhibitors is considered a serious adverse drug reaction (SADR). The sampling time points and inhibitor levels should be recorded and included in the SADR report. For SADR reporting requirements, see Section 8.2.4.

Thromboembolic events

A sample CRF for thromboembolic events is provided in the Appendix 1: Case Safety Report Form, Case Safety Report Form - Annex 3: Thromboembolic Events.

8.2.4 Reporting of adverse drug reactions (ADRs) and other safety information

All suspected ADRs and other safety information associated with the administration of *Nuwiq*® have to be reported in the Case Safety Report Form and be sent to:

Octapharma Central Drug Safety Unit
OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
[redacted]

Reporting requirements for SADRs

SADRs have to be reported immediately by fax or email (within 24 hrs). Non-serious ADRs and other safety information should be reported to Octapharma upon recognition but no later than 10 days after their occurrence.

Patients who carry out home-treatment should be asked to immediately inform the treating physician of any ADR or other relevant safety information. The treating physician has to assess the causal relationship for ADRs and report ADRs and other relevant drug safety information.

For information about possible ADRs and other safety information, please refer to the local Summary of Product Characteristics of *Nuwiq*®.

8.3 Optional PK evaluation

Individual dosing and dosing interval can be calculated at the beginning or during patients are on this study if deemed potentially beneficial by the treating physician. The treating physician can decide whether an individual or population approach will be used to perform the PK analysis. For the PK evaluation the information listed in Table 5 should be collected.

Table 5 Flow Chart of Assessments Performed for Individual or Population based PK Analysis

Individual PK	Population PK
- Current body weight	- Current body weight - Current height
- FVIII:C levels measured locally or centrally (as applicable per country) before and at least 5 times after *Nuwiq*® infusion of a recommended dose of 60±5 IU/kg. - The following time points are recommended: • Before (≤ 30 min) infusion of *Nuwiq*® • 30 minutes, 6, 24, 48 and 72 hours after infusion of *Nuwiq*® • For a complete PK additionally 1, 3, 9 and 30 hours after the infusion are recommended.	- FVIII:C levels measured locally or centrally (as applicable per country) at 1 to 3 time points* (prior and) after infusion of *Nuwiq*®. Sampling time points can be combined from multiple infusions of *Nuwiq*® at a dose patient is routinely treated with. - The following time points for the determination of FVIII plasma levels are recommended: • 1-3 time points at least 12h apart between 4-48h. Example: between 4-8h (e.g. 6h), 16-28h (e.g. 24h†) and 40-60h (e.g. 48h) §

*inclusion of a pre-infusion sample is recommended.
†24h is the sample providing the most information.
§ If patient is known to have a longer half-life with *Nuwiq*®, a sample between 60 and 84h is recommended (e.g. 72h).

- FVIII:C levels measured after infusion of *Nuwiq*® up to 6 months prior to enrolment in the study are acceptable to perform the PK analysis, if no significant changes in patient's health or weight have been recorded .

- Patients must consent to this optional assessment.

- Patients should be preferably not bleeding at the time of blood sampling for PK.

8.4 Laboratory Assessments

8.4.1 General Laboratory Assessments

General laboratory assessments, such as FVIII:C measurements in case of surgery will be done by the **local laboratories**.

FVIII:C measurement for PK analysis will be done either at local laboratories or central laboratory as applicable per specific countries.

8.4.2 Immunogenicity

The occurrence of antibodies against FVIII is a major complication of haemophilia A treatment. The risk of inhibitor occurrence is higher in patients with severe haemophilia A than in patients with moderate and mild disease, and the genotype (high risk: inversions, large deletions or nonsense mutations of the FVIII gene) and ethnic background of the patient is also of relevance.

In addition, risk may be associated with commencing treatment in previously untreated patients, when changing treatment, or when the antigenicity of a product has been altered due to changes in the manufacturing process.

Previously treated patients, the population to be enrolled into this study, are the most suitable candidates to test the product-related immunogenicity of a factor VIII product (Guideline EMA/CHMP/BPWP/144533/2009).

- According to Guideline EMA/CHMP/BPWP/144533/2009, there should not be any clinical suspicion of inhibitors before inclusion into the study, and a recovery and inhibitor test in a **central laboratory** should confirm that the patient is inhibitor-negative at study entry.
- In addition, testing should be carried out if there is any suspicion of an inhibitor.
- Inhibitor tests should be performed when the plasma factor VIII level has reached a pre-substitution nadir (documentation for the last infusion should be provided).
- Inhibitor re-testing using a second separately drawn sample as confirmatory measurement should be performed in the central laboratory.
- The flow chart of inhibitor testing is as recommended by Guideline EMA/CHMP/BPWP/144533/2009 is given in Table 3.

FVIII inhibitors will be assessed by the following central laboratory using validated test:

Esoterix Coagulation
8490 Upland Drive
Suite 100
Englewood, Colorado 80112, USA

FVIII inhibitor test used

Inhibitor activity will be determined by the modified Bethesda assay (Nijmegen modification).

FVIII inhibitor status definitions

The FVIII inhibitor status is defined as follow:

- Negative: < 0.6 BU
- Low-titre inhibitors: < 5 BU
- High-titre inhibitors: ≥ 5 BU

A rise in the circulating FVIII level of less than 1% per FVIII IU/kg administered will be considered an indication for inhibitor development. A rise of less than 1.5% per IU/kg administered will be considered suggestive for inhibitor development.

The flow chart of FVIII inhibitor testing as recommended by Guideline EMA/CHMP/BPWP/144533/2009 is given in Table 3.

The occurrence of FVIII inhibitors is considered a serious adverse drug reaction (SADR). The sampling time points and inhibitor levels should be recorded and included in the SADR report. For SADR reporting requirements, see Section 8.2.4.

9 DATA MANAGEMENT

9.1 Documentation of Data

For each patient enrolled, a Case Report Form (CRF) will be completed and approved by the treating physician or other authorised personnel. Study site staff will be responsible for entering all patient data into the CRF.

If any errors in the CRFs are found during the data review process, queries will be generated by either a monitor or Data Management and submitted to the site personnel or monitor. Once the query has been answered, Data Management or the monitor will review the new or changed data to ensure an appropriate response and close the query.

9.2 Responsibilities

The treating physician is accountable for the conduct of the study. On request, the treating physician will supply the Sponsor with additional data relating to the study, ensuring that the patient's confidentiality is maintained. This is particularly important when errors in data transcription are encountered. In case of particular issues or queries by regulatory

authorities, it is also necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

10 DATA ANALYSIS

The statistical analysis will be delegated under an agreement of transfer of responsibilities to an external Contract Research Organization (CRO). The CRO has to comply with all Octapharma procedures and policies. Discrepancies or exceptions are to be approved by the Sponsor's Manager of Biometrics.

10.1 Determination of Sample Size

No formal sample size determination was performed. According to Guideline EMA/CHMP/BPWP/144533/2009, the number of patients typically needed in a post-authorisation study with FVIII to cover immunogenicity aspects is 200.

10.2 Analysis Plan

The data recorded in the CRF will be analysed using descriptive statistical methods. An analysis plan detailing the analyses to be performed will be prepared by the study statistician and approved by the Sponsor before the start of the study.

10.3 Progress Study Reports

A progress study report will be prepared 2 years after marketing authorisation, detailing the recruitment status and progress of the study.

10.4 Optional PK evaluation

Individual PKs will be assessed based on the availability of individual patient data using either a 1- or 2-compartment model or the WAPPS-Hemo (Web-Accessible Population Pharmacokinetics Service Hemophilia) model. Based on the estimated PK parameters, potential treatment options will be calculated. The calculated PK parameters will be analysed descriptively.

11 ETHICAL AND REGULATORY ASPECTS

11.1 Ethical and Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki and applicable national requirements for non-interventional studies.

11.2 Submission of Study Documents to IEC and/or Regulatory Authority

If required by national regulations pertaining to the performance of non-interventional studies, the study protocol, a sample of the patient information and informed consent form, any other materials provided to the patients, and further requested information will be submitted by the Sponsor or the treating physician to the appropriate IEC and/or the Regulatory Authority.

The Sponsor, the treating physician, and any third party (e.g., CRO) involved in notifying the IEC and/or Regulatory Authority must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

11.3 Patient Information and Informed Consent

The treating physician will obtain freely given written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the study that are relevant to the patient's decision to participate. The informed consent form must be signed, with the patient's name and the date and time added by the patient, before the patient is exposed to any study-related procedure, including screening for eligibility.

For patients not qualified to give legal consent, written consent must be obtained from the legal guardian.

The treating physician will explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify. The treating physician will complete the informed consent section of the CRF for each patient enrolled.

Each patient will be informed that his medical (source) records may be reviewed by the study monitor, a quality assurance auditor, or a health authority inspector in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

11.4 Protocol Amendments

Any amendments will be submitted to the IEC(s) and/or competent authority if required by national regulations.

11.5 Confidentiality of Patient Data

The treating physician will ensure that the patient's confidentiality is preserved. On CRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient code (see Section 7.3). Documents not intended for submission to the Sponsor, i.e., a confidential patient identification code list, original consent forms, and patient records, will be maintained by the treating physician in strict confidence.

12 REPORTING AND PUBLICATION

12.1 Final Study Report

A final study report (in accordance with relevant guidelines and the Sponsor's SOPs) will be prepared by the Sponsor after completion of the study.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is envisaged by a physician, the physician agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor prior to submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the author.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multicentre studies only in their entirety and not as individual centre data. Authorship will be determined by mutual agreement.

13 REFERENCES

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APPENDIX

Appendix 1: Case Safety Report Form

octapharma

Local Log Number _____

Case Safety Report Form

Page 1 of 4

Report version	Dates	Report source / type
☐ Initial	Date initially received (dd/mm/yy) [1]:	☐ Non-Interventional study (Study ID:GENA-99)
☐ Follow-up #	Date new information (FU) received (dd/mm/yy):	☐ Pregnancy (please complete Pregnancy Report Form)
	Country of Event:	☐ Misuse/abuse/overdose ☐ Off-label-use ☐ Other:

1. REPORTER

Reporter	Company reporter
Name: Institution: Address: Telephone: Fax: Email: ☐ Physician ☐ Pharmacist ☐ Nurse ☐ Other:	Name: Institution: Address: Telephone: Fax: Email: ☐ Drug Safety ☐ Sales Representative ☐ Other

2. PATIENT INFORMATION

Initials[2].	Date of Birth (dd/mm/yy):	Height (cm):	Race:
☐ Male ☐ Female ☐ Pregnant week of gestation:	Age: Age Group[3]:	Weight (kg):	☐White ☐Black or African American ☐Asian ☐American Indian or Alaska Native ☐Native Hawaiian or other Pacific Islander ☐Other:_____ Ethnicity: ☐Hispanic or Latino ☐Not Hispanic or Latino

3. SUSPECT PRODUCT(S) [4]

Product /Generic name and Batch No	Conc. of solution	Route	Treatment dosage/ Infusion rate	Start/End	Duration	Indication

Overall treatment regimen with suspect drug(s) (incl. start, frequency, dates):

4. ADVERSE REACTION* [5]

* If **inhibitor development is SUSPECTED**, please be sure to also **complete Annex 1**.
If a **hypersensitivity/anaphylactic reaction is SUSPECTED**, please be sure to also **complete Annex 2**.
If a **thromboembolic event is SUSPECTED**, please be sure to also **complete Annex 3**.

Case Safety Report Form Human-cl rhFVIII

octapharma

Local Log Number _____

Case Safety Report Form

Adverse Event/ Diagnosis	Severity	Date (start/end)	Duration (incl Units)	Latency [6] (incl Units)	Outcome
	☐mild ☐moderate ☐severe				☐Recovered ☐Resolving ☐Recovered with sequelae ☐Fatal ☐Unknown
	☐mild ☐moderate ☐severe				☐Recovered ☐Resolving ☐Recovered with sequelae ☐Fatal ☐Unknown
	☐mild ☐moderate ☐severe				☐Recovered ☐Resolving ☐Recovered with sequelae ☐Fatal ☐Unknown
Did reaction(s) stop after stopping suspect product [7]?		☐Yes ☐No ☐Unknown ☐NA			
Action taken with respect to suspect product(s)?		☐Drug(s) withdrawn ☐None ☐Unknown			
Did reaction(s) reappear after reintroduction?		☐Yes ☐No ☐Unknown ☐NA		Date(s):	
Did patient receive previous treatment with suspect product(s) or similar product(s)?		☐Yes ☐No ☐Unknown ☐NA			
Did patient experience previous adverse reactions with suspect product(s) or similar product(s) [8]?		☐Yes ☐No ☐Unknown ☐NA		If yes, please provide information (dates, type(s) of reaction & other relevant details in Section 9 Detailed Description of Event)	

Remedial Therapy [9] ☐None ☐Unknown ☐Yes, please specify below

Laboratory tests performed [10] ☐None ☐Unknown ☐Yes, please specify below

5. CONCOMITANT ILLNESSES AND DISEASES (E.G. ALLERGY, HISTORY, ALCOHOL ABUSE, ETC.)

☐None ☐Unknown ☐Yes, please specify below

6. CONCOMITANT MEDICATION [11]

☐None ☐Unknown ☐Yes, please specify below

octapharma

Local Log Number _____

Case Safety Report Form

Page 3 of 4

7. CASE REPORT CLASSIFICATION / SERIOUSNESS CRITERIA[12]

Case report: ☐ non-serious ☐ serious (please complete section below) ☐ NA

☐Patient hospitalized Date: from to ☐Hospitalization prolonged Date: from to ☐Life threatening ☐Fatal ☐Resulting in persistent or significant disability/incapacity ☐Resulting in congenital anomaly or birth defect ☐Suspected transmission of an infectious agent ☐Other:	Date of death: Autopsy: ☐Yes ☐No ☐Unknown Cause of death:

8. POSSIBLE CAUSE(S) OF REACTION(S) / CAUSALITY ASSESSMENT

Reporter

☐Suspect drug(s) ☐Underlying disease ☐Lack of efficacy/worsening of treated conditions
☐Concomitant medication ☐Administration-related ☐Other:

Causality assessment: (i.e. Relatedness of reaction to administration of suspected Octapharma drug)

☐Reaction is possibly related ☐Reaction is unlikely related ☐Unknown
Comment:

Company reporter

☐Suspect drug(s) ☐Underlying disease ☐Lack of efficacy/worsening of treated conditions
☐Concomitant medication ☐Administration-related ☐Other:

Causality assessment: (i.e. Relatedness of reaction to administration of suspected Octapharma drug)

☐Reaction is possibly related ☐Reaction is unlikely related ☐Unknown
Comment:

9. DETAILED DESCRIPTION OF EVENT[13]

10. OTHER COMMENTS [14]

Was Competent Authority(ies) informed? ☐No ☐Unknown ☐Yes, Authority reference #

Has more information been requested from the reporter? ☐Yes ☐No

Is adverse reaction(s) expected according to local product package insert? ☐Yes ☐No
Comment:

On behalf of Octapharma: Print Name Date, Signature	Original Reporter: Print Name Date, Signature

Case Safety Report Form Human-cl rhFVIII

octapharma

Local Log Number _____

Case Safety Report Form

[1] To prevent errors resulting from differently used date formats, please state all dates in the format DD/MM/YY

[2] Initials should be in the format "First name/Surname".

[3] Age group: neonate (up to 1 month), infant (> 1 month to < 2 years), child (> 2 years to < 12 years), adolescent (> 12 years to < 16 years), adult (> 16 years to < 65 years), elderly (> 65 years)

[4] Information on treatment that led to the adverse reaction(s) (generally last treatment). If product(s) were taken regularly please enter information in the section below.

[5] The diagnosis/adverse reaction(s) should be stated by the initial reporter. A diagnosis is preferred and the associated events should be described in section **9** Detailed Description of Event

[6] Time since beginning of last treatment with suspect drug(s) which resulted in adverse reaction(s).

[7] Dechallenging information refers to the situation where a direct response (i.e. improvement of adverse reaction(s)) could be noted without patient receiving remedial therapy.

[8] If patient experienced adverse reaction(s) with Octapharma product(s) previously, this may be considered a separate case safety report. Please provide as much information as possible under section **9** Detailed Description of Event.

[9] Provide information on therapy to treat adverse reaction(s). For drugs please include tradename, active ingredient, dosage, route, start/end dates.

[10] Any tests relating to the adverse reaction(s) including results, units, normal range.

[11] Other medication the patient received prior to the adverse reaction(s) or at the time of suspect drug(s) administration including trade name, active ingredient, dosage, route, frequency, indication for use.

[12] The seriousness criteria should not be confused with the nature/degree of the adverse reaction(s) but determines the timeframe of regulatory reporting based on the criteria specified in the section below.

[13] A detailed description of the chronology and outcome of the adverse reaction(s).

[14] Any other information that may be of interest or if available space in the form is insufficient.

Case Safety Report Form - Annex 1: FVIII Inhibitor Development

FVIII Inhibitor development **Follow-up questionnaire** **Local log number:** _____

FVIII Inhibitor development

A. Patient Information

Patient number _____ **Patient Initials:** ☐☐ (First/Last) **Date of birth:** ☐☐☐☐☐☐☐☐ d d m m y y y y

B. Patient History

Family history of haemophilia: ☐No ☐Yes* ☐Unknown

*If yes, please specify: _____

Family history of inhibitors: ☐No ☐Yes ☐Unknown

Type of FVIII gene mutation: _____

Does patient have a history of FVIII inhibitors? ☐No ☐Yes*

*If yes, date the inhibitor was first detected: ☐☐☐☐☐☐ d d m m y y

Inhibitor developed while patient was on (name of product): _____

Estimated number of exposure days before inhibitors developed: ☐☐

Treatment :
- ☐ Switch of product
- ☐ Initiation of ITI
- ☐ Other
- ☐ No treatment

Result of the treatment: _____

Viral and infection status:

Has the patient had any of the following infections?

Hepatitis A:	☐ Yes	☐ No	☐ Unknown
Hepatitis B:	☐ Yes	☐ No	☐ Unknown
Is the patient positive for anti-Parvovirus B19 antibodies?	☐ Yes	☐ No	☐ Unknown
Is the patient positive for anti-hepatitis C antibodies?	☐ Yes	☐ No	☐ Unknown
Is the patient HIV-positive?	☐ Yes	☐ No	☐ Unknown

Follow-up questionnaire

FVIII Inhibitor development **Local log number:** _____

Co-morbidity which may have a significant impact on blood coagulation or immune reactions? ☐ Yes* ☐ No ☐ Unknown

*If yes, please specify: _____

_____

Did the patient have any of the following in direct relationship to inhibitor development:

Infections ☐ No ☐ Yes

Allergic conditions ☐ No ☐ Yes

Vaccinations ☐ No ☐ Yes

Surgeries ☐ No ☐ Yes

Relevant life style information: _____

_____

Patient's general health status: ☐ Good ☐ Impaired*

*If impaired, please specify: _____

_____

C. Previous exposure to plasma derived/recombinant products

Previous exposure to plasma derived/recombinant products: ☐ Yes* ☐ No

*If yes, please specify: Product name _____ Batch number _____

Therapy date |_|_|_|_|_|_| (d d m m y y) Total exposure _____

Previous treatment has been well tolerated: ☐ Yes ☐ No*

*If no, please describe symptoms/treatment: _____

_____

_____

D. Current Drug exposure

Treatment with Human-cl rhFVIII started on: |_|_|_|_|_|_| (d d m m y y) **Treatment frequency:** _____

Total dose: _____ IU **Batch number:** _____

Follow-up questionnaire

FVIII Inhibitor development **Local log number:** _____

Does the patient take any concomitant medications? ☐No ☐Yes*

*If yes, please specify: Product name: _____ Start date: d d m m y y Stop date: d d m m y y

Product name: _____ Start date: d d m m y y Stop date: d d m m y y

Product name: _____ Start date: d d m m y y Stop date: d d m m y y

Product name: _____ Start date: d d m m y y Stop date: d d m m y y

E. Information on the ADR (inhibitor development)

Date inhibitor development was first suspected: d d m m y y

Reason(s) for clinical suspicion of inhibitor development:

☐ Higher dose than usual needed to prevent break-through bleeds
☐ More frequent prophylactic infusions than usual needed to prevent break-through bleeds
☐ Higher dose than usual needed to treat a bleeding episode
☐ Other, please specify: _____

Additional case information: _____

Inhibitor testing

Date of blood sampling: d d m m y y Time of blood sampling: h h m m ☐ Not done

☐ Local lab: . BU ☐ Central lab: . BU

Inhibitor re-testing by central lab in case of positive result on initial testing

Date of blood sampling: d d m m y y Time of blood sampling: h h m m ☐ Not done

☐ Central lab: . BU

FVIII Inhibitor development **Follow-up questionnaire** **Local log number:** _____

FVIII recovery testing

Pre-infusion FVIII:C activity testing

Date of blood sampling: ☐☐☐☐☐☐ (d d m m y y) Time of blood sampling: ☐☐☐☐ (h h m m) ☐ Not done

	Local lab:	Central lab:
1-stage clotting assay:	☐ ☐☐☐.☐ IU/dL	☐ ☐☐☐.☐ IU/dL
Chromogenic assay:	☐ ☐☐☐.☐ IU/dL	☐ ☐☐☐.☐ IU/dL

Human-cl rhFVIII infusion

Dose: ☐☐☐☐ IU Body weight: ☐☐☐ kg Dose/kg: ☐☐ IU/kg

Date of infusion: ☐☐☐☐☐☐ (d d m m y y) Start time: ☐☐☐☐ (h h m m) End time: ☐☐☐☐ (h h m m)

FVIII:C activity testing 15–45 minutes post-infusion

Date of blood sampling: ☐☐☐☐☐☐ (d d m m y y) Time of blood sampling: ☐☐☐☐ (h h m m) ☐ Not done

	Local lab:	Central lab:
1-stage clotting assay:	☐ ☐☐☐.☐ IU/dL	☐ ☐☐☐.☐ IU/dL
Chromogenic assay:	☐ ☐☐☐.☐ IU/dL	☐ ☐☐☐.☐ IU/dL

F. Outcome

Patient:
- ☐ continued with Human-cl rhFVIII treatment
- ☐ switched to other product
- ☐ continued with other treatment

G. Reporter's details

Name: _____ **Address:** _____

Date and signature: _____

Case Safety Report Form - Annex 2: Hypersensitivity/Anaphylactic Reactions

Hypersensitivity/Anaphylactic Reaction **Follow-up questionnaire** **Local log number:** _____

Hypersensitivity/Anaphylactic Reactions

A. Patient Information

Patient number _____ **Patient Initials:** ☐☐ (First/Last) **Date of birth:** ☐☐☐☐☐☐☐☐ d d m m y y y y

B. Patient History

☐ Asthma ☐ Cystic fibrosis ☐ Diabetes ☐ Autoimmune disease ☐ Chronic urticaria ☐ Other*

Allergic disease: ☐ Yes* ☐ No

*If yes, please specify: _____

*Please specify: _____

Have hypersensitivity/anaphylactic reactions been observed previously without the administration of Human-cl rhFVIII? ☐ Yes ☐ No

Drug reactions during previous surgery:	☐ Yes	☐ No	☐ Unknown
Reactions during previous vaccinations:	☐ Yes	☐ No	☐ Unknown
Family history of (drug) allergies:	☐ Yes	☐ No	☐ Unknown

C. Previous exposure to plasma derived/recombinant products

Previous exposure to plasma derived/recombinant products: ☐ Yes* ☐ No

*If yes, please specify: Product name _____ Batch number _____

Therapy date ☐☐☐☐☐☐ d d m m y y Total exposure _____

Previous treatment has been well tolerated: ☐ Yes ☐ No*

*If no, please describe symptoms/treatment: _____

D. Current Drug exposure

Treatment with Human-cl rhFVIII started on: ☐☐☐☐☐☐ d d m m y y **Treatment frequency:** _____

Total dose: _____ IU **Batch number:** _____

Follow-up questionnaire

Hypersensitivity/Anaphylactic Reaction **Local log number:** _____

Does the patient take any concomitant medications? ☐ No ☐ Yes*

*If yes, please specify:

Product name: _____ Start date: d d m m y y Stop date: d d m m y y

Product name: _____ Start date: d d m m y y Stop date: d d m m y y

Product name: _____ Start date: d d m m y y Stop date: d d m m y y

Product name: _____ Start date: d d m m y y Stop date: d d m m y y

E. Information on the ADR (hypersensitivity/anaphylactic reaction)

Signs and symptoms:

Cutaneous symptoms

☐ Exanthema	Start date: d d m m y y	
☐ Pruritus	Start date: d d m m y y	
☐ Hives	Start date: d d m m y y	
☐ Generalised urticaria	Start date: d d m m y y	
☐ Angioedema	Start date: d d m m y y	
☐ Other: _____	Start date: d d m m y y	

Gastrointestinal symptoms

☐ Nausea	Start date: d d m m y y
☐ Vomiting	Start date: d d m m y y
☐ Gastrointestinal cramps	Start date: d d m m y y
☐ Diarrhoea	Start date: d d m m y y
☐ Other: _____	Start date: d d m m y y

Respiratory symptoms

☐ Cough	Start date: d d m m y y
☐ Dyspnoea	Start date: d d m m y y
☐ Wheezing	Start date: d d m m y y
☐ Sneezing	Start date: d d m m y y
☐ Nasal obstruction	Start date: d d m m y y
☐ Other:	Start date: d d m m y y

Cardiovascular symptoms

☐ Tachycardia	Start date: d d m m y y
☐ Hypotension	Start date: d d m m y y
☐ Collapse	Start date: d d m m y y
☐ Arrhythmia	Start date: d d m m y y
☐ Other: _____	Start date: d d m m y y

Associated symptoms

☐ Fever	Start date: d d m m y y
☐ Malaise	Start date: d d m m y y
☐ Fainting	Start date: d d m m y y
☐ Paraesthesia	Start date: d d m m y y

☐ Sweating	Start date: d d m m y y
☐ Tightness of the chest	Start date: d d m m y y
☐ Other: _____	Start date: d d m m y y

Follow-up questionnaire

Hypersensitivity/Anaphylactic Reaction **Local log number:** _____

Management following the reaction:

- ☐ None
- ☐ Discontinue Human-cl rhFVIII
- ☐ Change to alternative drug
- ☐ Dose reduction
- ☐ Antihistamines
- ☐ Corticosteroids
- ☐ Bronchodilators
- ☐ Shock treatment
- ☐ Other: _____

Clinical outcome:

- ☐ Recovered without sequelae
- ☐ Recovered with sequelae
- ☐ Not recovered

Additional information:

_____

_____

F. Outcome

Patient:

- ☐ continued with Human-cl rhFVIII treatment
- ☐ switched to other product
- ☐ continued with other treatment

G. Reporter`s details

Name: _____ **Address:** _____

Date and signature: _____

Case Safety Report Form - Annex 3: Thromboembolic Events

Thromboembolic events **Follow-up questionnaire** **Local log number:** _____

Thromboembolic event

A. Patient Information

Patient number: _____ **Patient Initials:** ☐☐ (First/Last) **Date of birth:** ☐☐☐☐☐☐☐☐ d d m m y y y y

B. Patient History

Patient risk factors for thromboembolic events:

- ☐ Hypertension
- ☐ Hyperlipidaemia
- ☐ Hypercholesterolemia
- ☐ Diabetes mellitus
- ☐ Arrhythmia
- ☐ Immobilization
- ☐ Indwelling central catheter
- ☐ Dehydration or hypovolemia
- ☐ History of deep venous thrombotic episodes
- ☐ History of pulmonary embolism
- ☐ History of myocardial infarction
- ☐ Known history of cardiovascular or cerebrovascular disease
- ☐ Inherited or acquired thrombophilic disease
- ☐ Age above 65 years
- ☐ Obesity

Other _____

C. Previous exposure to plasma derived/recombinant products

Previous exposure to plasma derived/recombinant products: ☐Yes* ☐No

*If yes, please specify: Product name _____ Batch number _____

Therapy date ☐☐☐☐☐☐ d d m m y y Total exposure _____

Previous treatment has been well tolerated: ☐Yes ☐No*

*If no, please describe symptoms/treatment: _____

D. Current Drug exposure

Treatment with Human-cl rhFVIII started on: ☐☐☐☐☐☐ d d m m y y **Treatment frequency:** _____

Total dose: _____ IU **Batch number:** _____

Follow-up questionnaire

Thromboembolic events **Local log number:** _____

Does the patient take any concomitant medications? ☐ No ☐ Yes*

*If yes, please specify: Product name: _____ Start date: d d m m y y Stop date: d d m m y y

Product name: _____ Start date: d d m m y y Stop date: d d m m y y

Product name: _____ Start date: d d m m y y Stop date: d d m m y y

Product name: _____ Start date: d d m m y y Stop date: d d m m y y

E. Information on the ADR (thromboembolic event)

Blood clot, heart attack or stroke since last FVIII infusion: ☐ Yes ☐ No ☐ Unknown

Classification Arterial ☐ Both ☐
Venous ☐ Not classifiable ☐

Latency (period in days between last FVIII infusion and reaction occurence):

During infusion ☐ 1-3 days postinfusion ☐ Other _____
Within 2 hours ☐ 4-7 days postinfusion ☐
Same day ☐ >7 days postinfusion ☐

Diagnosis is based on:

Clinical symptoms ☐ Phlebography ☐ Wells or other score ☐
Laboratory (troponin, d-dimer, etc.) ☐ X-ray, CT, SPECT ☐ Other _____
Ultrasonography ☐ ECG ☐

F. Outcome

Patient: ☐ continued with Human-cl rhFVIII treatment
☐ switched to other product
☐ continued with other treatment

G. Reporter`s details

Name: _____ **Address:** _____

Date and signature: _____