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CLINICAL STUDY PROTOCOL

Extension Study for Patients who completed GENA-05 (NuProtect) – to Investigate Immunogenicity, Efficacy and Safety of Treatment with *Human-cl rhFVIII*

Investigational Product	*Human-cl rhFVIII*
Indication	Severe Haemophilia A
Study Design	Prospective, multicentre, multinational, open-label, non-controlled
Sponsor	Octapharma Pharmazeutika Produktionsges.m.b.H. Oberlaaer Strasse 235, A-1100 Vienna, Austria
Study Number	GENA-15
EudraCT and/or IND Number	2013-003997-28 BB-IND 13722
Development Phase	Phase IIIb
Planned Clinical Start	1st Quarter 2014
Planned Clinical End	1st Quarter 2016
Date of Protocol	18-Sep-2013
Version	01
Co-ordinating Investigator	[redacted]

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STUDY OUTLINE

Name of Sponsor/Company: Octapharma Pharmazeutika Produktions GmbH, Vienna, Austria	
Name of Investigational Product: *Human-cl rhFVIII*	Protocol Identification Code: GENA-15
Name of Active Ingredient: Coagulation FVIII	Date of Final Protocol: 18-Sep-2013
Title of Study: Extension Study for Patients who completed GENA-05 (NuProtect) – to Investigate Immunogenicity, Efficacy and Safety of Treatment with *Human-cl rhFVIII*	
Indication: Severe Haemophilia A (FVIII coagulation activity [FVIII:C] <1%)	
Number of Study Centre(s): Around 20-30 centres worldwide are planned to participate in this study	
Study Duration: This study is planned to start in the 1st quarter 2014 and will be completed by 1st quarter 2016 at the latest	**Development Phase:** IIIb
Objectives: • To investigate the immunogenicity of *Human-cl rhFVIII* in patients who completed GENA-05 in accordance with the study protocol • To assess the efficacy of *Human-cl rhFVIII* during prophylactic treatment (based on the frequency of spontaneous break-through bleeds) • To assess the efficacy of *Human-cl rhFVIII* during treatment of bleeds • To assess the efficacy of *Human-cl rhFVIII* in surgical prophylaxis • To assess the safety and tolerability of *Human-cl rhFVIII*	
Study Design: Prospective, multicentre, multinational, open-label, non-controlled	
Number of Patients: Only patients who completed GENA-05 in accordance with the study protocol may be enrolled (max. 100)	
Patient Selection Criteria: The patient population will mainly be young children; however, there was no age limitation in the preceding GENA-05 study. *Inclusion criteria:* 1. Patients who completed GENA-05 in accordance with the study protocol 2. Voluntarily given, fully informed written and signed consent obtained before any study-related procedures are conducted (obtained from the patient's parent/legal guardian) *Exclusion criteria:* 1. Severe liver or kidney disease (alanine amino transferase (ALT) or aspartate transaminase (AST) levels >5 times of upper limit of normal, creatinine >120 µmol/L); 2. Concomitant treatment with any systemic immunosuppressive drug; 3. Other FVIII concentrate than *Human-cl rhFVIII* was received between completion visit of GENA-05 and start of GENA-15 (except emergency cases).	
Test Product, Dose, Mode of Administration, and Batch Number(s): *Human-cl rhFVIII* is a purified B-domain deleted FVIII glycoprotein that is synthesised	

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by a genetically engineered human embryonic kidney cell line (HEK 293F). *Human-cl rhFVIII* will be provided in single use vials containing a nominal potency of 250, 500, 1000 or 2000 International Units (IU) each of freeze-dried recombinant FVIII (rFVIII) concentrate to be reconstituted in 2.5 mL of water for injection.

Human-cl rhFVIII is to be used as intravenous injection only (maximally 4 mL/minute).

Dose:

Prophylactic treatment is recommended. However, the Investigator will have final discretion whether patients will be treated prophylactically or on-demand. Patients may switch from on-demand to prophylactic treatment, or from prophylactic to on-demand treatment during the course of the study.

Prophylactic treatment:

Patients will be treated prophylactically with a recommended dose of >20 IU FVIII/kg body weight (BW). The frequency of treatment will depend on the patient's clinical situation. In cases of inadequate response, *Human-cl rhFVIII* administration frequency or dose adjustments can be made at Investigator's discretion.

On-demand treatment:

In case of a bleed, the patients can be treated on-demand. The dosage and duration of treatment of spontaneous or traumatic bleeds depend on the location and the extent of the bleeding as well as on the clinical situation of the patient. Dosage recommendations are given as follows:

- Minor haemorrhage: 20-30 IU FVIII/kg BW to achieve an intended target peak level of about 40% to 60%. Repeat dose every 8-24 hours until BE is resolved.
- Moderate to major haemorrhage: 30-40 IU FVIII/kg BW to achieve an intended target peak level of about 60% to 80%. Repeat dose every 6-24 hours until BE is resolved.
- Major to life-threatening haemorrhage: initial dose of 50-80 IU FVIII/kg BW to achieve an intended target peak level of 100% to 120%. Repeat dose of >20 IU FVIII/kg BW every 6-12 hours until BE is resolved.

Surgical prophylaxis:

The dosage and duration of treatment with *Human-cl rhFVIII* will depend on the type of surgery and the patient's individual incremental recovery. Dosage recommendations are given as follows:

- Minor surgeries including tooth extractions: 25-30 IU FVIII/kg BW starting within 3 hours prior to surgery to achieve an intended target peak level of >30%. Repeat one dose every 12-24 hours if needed. Trough levels should be maintained at ≥ 30%.
- Major surgeries: > 50 IU FVIII/kg BW within 3 hours prior to surgery to achieve an intended target peak level of approximately 100%. Repeat if necessary after 6-12 hours initially and for at least 6 to 14 days until healing is complete and recurrence to regular prophylactic treatment is possible. Trough levels should be maintained at > 50%.

Batch Number(s):

Several batches of *Human-cl rhFVIII* will be used.

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Name of Investigational Product: *Human-cl rhFVIII*	Protocol Identification Code: GENA-15
Name of Active Ingredient: Coagulation FVIII	Date of Final Protocol: 18-Sep-2013
Duration of Treatment: The patients are planned to stay in the study until the IMP is registered and launched in the individual countries, or for a maximum period of 2 years from screening, whichever comes first.	
Reference Therapy, Dose, Mode of Administration, and Batch Number(s): Not applicable	
Study Outcome Parameters / Endpoints): Immunogenicity: Inhibitor activity will be determined by the modified Bethesda assay (Nijmegen modification), using congenital FVIII-deficient human plasma spiked with *Human-cl rhFVIII* at the following time points: • At Screening Visit, which can be the same sampling time-point as the completion visit of GENA-05 • Once every 6 months during the open treatment phase • At study completion • Any time in the case of suspicion of inhibitor development. In case of a positive inhibitor result, an inhibitor re-test using a second separately drawn sample should be performed, centrally. Efficacy: *Efficacy of prophylactic treatment:* The efficacy of *Human-cl rhFVIII* in the prophylactic treatment will be assessed based on the frequency of spontaneous break-through bleeds under prophylactic treatment. The dates and times of study drug infusions, details of dose(s) and product batch numbers used for the prophylactic treatment will be documented. Details of any BEs occurring under prophylactic treatment will be documented. Study drug consumption data (FVIII IU/kg per month, per year) per patient and in total will be evaluated. *Efficacy of treatment of bleeds:* The efficacy of *Human-cl rhFVIII* in the treatment of bleeds will be assessed based on an objective haemostatic efficacy scale. Details of the bleed (type, site and severity of the bleed, and the start and end date and time of the bleed), the amount of *Human-cl rhFVIII* needed and the number of injections necessary to stop the bleed will be documented. *Efficacy of surgical prophylaxis*: The efficacy of *Human-cl rhFVIII* in surgical prophylaxis will be assessed based on: • Overall efficacy assessment (taking the intra- and post-operative assessment into account) after the end of the surgical prophylactic treatment phase, done together by the surgeon and the haematologist. • Average and maximum expected estimated blood loss compared to the actual estimated blood loss. In addition, the location, severity, and type of surgery will be documented. Expected and actual duration of surgical procedure and details of administered dose(s) of *Human-cl rhFVIII* (pre-, intra- and/or post-operatively) will be recorded. FVIII plasma levels (pre-, intra-, and post-operatively) will be measured. Details of concomitantly administered products (except standard anaesthetics) along with a brief narrative describing the	

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outcome of the intervention will be recorded.

Safety:

Vital signs: Blood pressure, heart rate, respiratory rate and body temperature will be assessed at screening, thereafter every 6 months (±2 weeks) and at study completion. In case IMP is injected at study site during these visits, one pre- and one post-treatment measurement is obligatory.

Safety laboratory parameters: The following routine safety laboratory parameters will be tested at screening (GENA-05 study completion values can be copied), at 6-monthly (± 2 weeks) follow-up visits, and at completion visit: haematological parameters (red blood cell count, white blood cell count, haemoglobin, haematocrit, platelet count) and clinical chemistry (ALT, AST, serum creatinine). Samples are analysed in the local laboratory.

Tolerability: The occurrence of any adverse event (AE) will be monitored throughout the study.

Summary of Study Procedures and Statistical Analysis Plan:

Study Procedures:

All administrations of *Human-cl rhFVIII*, the occurrence of bleeds, the occurrence of AEs and the administration of concomitant medication during the entire study period will be thoroughly documented to assess the exposure to FVIII, the efficacy in the prevention of and the treatment of bleeds, and the overall safety and tolerability.

Screening Visit:

Patients' parent(s)/legal guardian(s) will be informed about the study details and will be required to give written informed consent before any investigations and any assessments can be performed. The majority of data required will be available from the preceding GENA-05 study, so that only the following information needs to be documented/assessed:

- Check of inclusion- and exclusion criteria
- Height
- Body weight

The Investigator will hand out the patient diary and instruct the patient/legal guardian how to document details of treatment with *Human-cl rhFVIII*, bleeds, AEs and concomitant medication. The patient/legal guardian will receive a sufficient amount of study product for home treatment and will be instructed on proper storage and administration. Details of home treatment (e.g. parents' home treatment training, the involvement of a general practitioner or a study nurse) are documented.

6-Monthly (± 2 weeks) Follow-Up Visits:

These visits will include additional investigations, i.e. assessment of safety laboratory parameters and – in case IMP is injected after blood sampling – vital signs pre- and 30-60 minutes post-injection.

At such visits, patients' body weight will be checked, and blood samples will be obtained for FVIII inhibitor screen (after a wash-out period of at least 2, but preferably 3 days after the previous IMP administration). The patient diary will be reviewed and data will be transferred into the CRF. The occurrence of AEs and changes in concomitant medication will be checked and documented. A physical examination is performed.

Surgical Visits:

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Study subjects may undergo surgical interventions during the course of the study. Depending on the type of surgery, subjects may or may not be hospitalised (in case of certain minor surgeries with low risk of post-operative bleeding) at the discretion of the Investigator. Details of surgery, *Human-cl rhFVIII* dosing, expected and actual blood loss, concomitant treatment (including need for additional blood transfusions), and lab investigations will be documented, as well as details of hospitalisation (start and end date, regular ward, intensive care unit stay).

Completion Visit:

For each patient, the study will be completed once the IMP is registered and launched in the respective country, but no later than 2 years from the screening visit.

At these visits, patients' body weight will be checked, and blood samples will be obtained for FVIII inhibitor screen (after a wash-out period of at least 2, preferably 3 days after the previous IMP administration) and for the safety panel. Vital signs will be checked and a physical examination will be performed. The occurrence of AEs and changes in concomitant medication will be checked and documented.

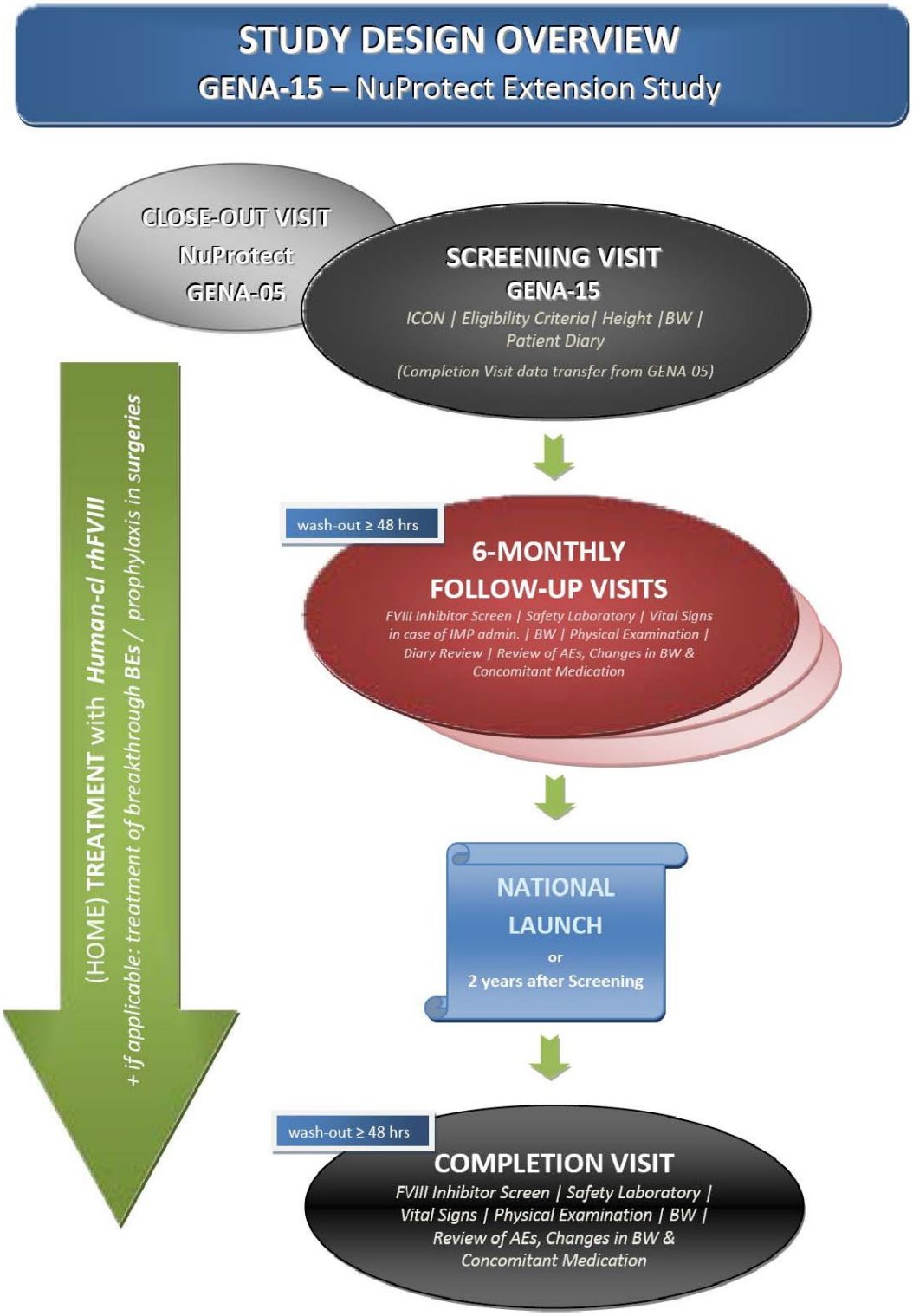
At this visit, the patient diary will be reviewed and data transferred into the CRF.

Statistical Analysis:

No inferential analysis involving formal testing is planned in this non-controlled trial. The patients are offered to continue treatment after the completion of the preceding GENA-05 study in accordance with the study protocol; no formal sample size estimation is performed. The statistical analyses of the endpoints will be descriptive.

The study assessments and scheduled time points are summarised in the Flow Chart:

FLOW CHART



PROTOCOL SIGNATURES

Signature of the Sponsor's Representative

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and the applicable regulatory requirements.

On behalf of the Sponsor

Signature of the Vice President Clinical Research &Development Haematology

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and the applicable regulatory requirements.

Signature of the Author of the Protocol/ Clinical Project Manager

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and the applicable regulatory requirements.

Signature of the Biostatistician

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and the applicable regulatory requirements.

Signature of the Coordinating Investigator

This study is intended to be conducted in compliance with the protocol,
Good Clinical Practice and the applicable regulatory requirements.

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LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate transaminase
BE	Bleeding episode
BLEED	Study population of BEs
BMI	Body mass index
BU	Bethesda unit
BW	Body weight
CHO	Chinese hamster ovary (cells)
CHR	Chromogenic
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
CVAD	Central Venous Access Device
ED	Exposure day
EMA	European Medicines Agency
FVIII	Coagulation factor VIII
FVIII:C	Factor VIII coagulation activity
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HEK	Human Embryonic Kidney
HLA	Human Leukocyte Antigen
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITI	Immune tolerance induction
ITT	Intention to treat
IU	International Unit
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
OC	Observed cases
OS	One-stage
PBMC	Peripheral blood mononuclear cells
PP	Per protocol
PROPH	Study population of subjects with prophylaxis
PTP	Previously-treated patient
PUP	Previously-untreated patient
RBC	Red blood cell
rFVIII	Recombinant FVIII
SAEs	Serious adverse events
SAP	Statistical analysis plan
SOC	System organ class
SOP	Standard operating procedure
SURG	Study population of surgeries
ULN	Upper limit of normal
WBC	White blood cell
WFI	Water for injection

1 INTRODUCTION

Haemophilia A is an inherited gender-related coagulation disorder in which affected males do not produce functional coagulation factor VIII (FVIII) in sufficient quantities to achieve satisfactory haemostasis. Therefore, patients suffer from bleeding diathesis. Most bleeding episodes (BEs) occur in joints and muscles. Without adequate treatment these 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, eyes and the retro-peritoneum. Hence, affected patients are at high risk to develop major and life-threatening bleeds after surgical procedures, even after minor ones such as tooth extraction.

The optimal effective treatment of the disorder is the replacement of FVIII by using FVIII concentrate either obtained by fractionation of human plasma or manufactured by recombinant DNA technology.

All commercially available recombinant rFVIII concentrates are exclusively produced in hamster cells, either in baby hamster kidney (BHK) cells (e.g. Kogenate FS) or in Chinese hamster ovary (CHO) cells (e.g. Advate, ReFacto). The intrinsic immunogenicity of current rFVIII products may be increased due to incorporation of non-human glycan structures during post-translational protein processing in mammalian cell lines.

Human-cl rhFVIII is a B-domain deleted rhFVIII expressed in genetically modified human embryonic kidney (HEK) 293F cells. Using a human cell line for the expression of rFVIII ensures that non-human immunogenic epitopes are absent, in contrast to rFVIII expressed in hamster cells. For example, N-glycolylneuraminic acid, which is reported to be antigenic in man (1) and present in recombinant glycoproteins expressed by CHO cells (2), was not detected in *Human-cl rhFVIII*. Furthermore, the antigenic carbohydrate epitope Galα1,3Gal, which has been reported to be present in recombinant proteins such as full-length FVIII from BHK cells (3), is not present in *Human-cl rhFVIII* either (4). The use of a human cell-line for the expression of rFVIII is expected to provide a more genuine human glycosylation pattern than achieved with murine cell-lines. This may result in an improved function and reduced immunogenicity of the rFVIII expressed from human cell-lines.

Clinical data on efficacy and safety of *Human-cl rhFVIII* in the targeted indications in adult and paediatric previously treated patients (PTPs) are available. Since previously untreated patients (PUPs) may respond differently to FVIII treatments than PTPs, European Medicines Agency (EMA) CHMP guidelines (5) specify that the clinical development strategy for FVIII products in paediatric patients should follow a stepwise approach, in order to gain experience in older patients before investigations are initiated in younger patients and finally in previously untreated patients. The ongoing study GENA-05 is assessing immunogenicity, efficacy and safety of *Human-cl rhFVIII* in previously untreated patients (PUPs) with severe Haemophilia A.

A summary of findings from non-clinical as well as clinical investigations can be found in the Clinical Investigator's Brochure.

1.1 Rationale for Conducting the Study

The present study has been designed to investigate the long-term immunogenicity, tolerability and efficacy of *Human-cl rhFVIII* in patients originally included into the preceding study GENA-05 as PUP (previously untreated patients) with severe Haemophilia A (FVIII:C <1%). Study participation is offered to all subjects who completed the foregoing GENA-05 study in

accordance with the study protocol, provided the IMP is not registered and ready for launch in the respective country. However, the maximum study participation is two years from time of screening.

GENA-15 is a prospective, open-label, uncontrolled, international, multi-centre Phase IIIb study with the objective of collecting long-term data on the immunogenicity, tolerability and efficacy of *Human-cl rhFVIII.*

Participation will be offered to all GENA-05 subjects who meet the eligibility criteria and are willing to continue prophylactic or on-demand treatment with *Human-cl rhFVIII* until they can switch to marketed product.

Dose Rationale

Human-cl rhFVIII will be provided in single use vials containing a nominal potency of 250, 500, 1000 or 2000 International Units (IU) each of freeze-dried rFVIII concentrate to be reconstituted in 2.5 mL of water for injection (WFI). *Human-cl rhFVIII* is to be used as intravenous injection only (maximum infusion speed: 4 mL/minute).

Dose and frequency adjustments are based on the individual patients' needs and are subject to the Investigators' clinical judgement.

1.2 Benefit-Risk Statement

On the basis of data already available for adults and children (PTPs), the half-life and the recovery of *Human-cl rhFVIII* are similar to other already licensed rFVIII preparations. It can be concluded that *Human-cl rhFVIII* is efficacious in the prevention and in the treatment of BEs and during surgical prophylaxis in patients with inherited FVIII deficiency.

Comparable to other rFVIII preparations, the following adverse drug reactions (ADRs) may occur when using *Human-cl rhFVIII*:

1. Allergic or anaphylactic types of reactions. Observed symptoms may include fever, chills, nausea, urticaria, pruritus, dizziness, chest tightness, shortness of breath, and – very rarely – anaphylactic shock.
2. Development of antibodies (inhibitors) against FVIII.

In conclusion, the hitherto existing clinical and pre-clinical data allow the conclusion that participating in this study does not represent any additional risk for the included patients in terms of immunogenicity and safety.

2 STUDY OBJECTIVES

Objectives of this trial are:

- To investigate the immunogenicity of *Human-cl rhFVIII* in patients who completed GENA-05 in accordance with the study protocol
- To assess the efficacy of *Human-cl rhFVIII* during prophylactic treatment (based on the frequency of spontaneous break-through bleeds)
- To assess the efficacy of *Human-cl rhFVIII* during treatment of bleeds
- To assess the efficacy of *Human-cl rhFVIII* in surgical prophylaxis

3 INVESTIGATIONAL PLAN

3.1 Study Endpoints

Immunogenicity of *Human-cl rhFVIII*

Inhibitor activity will be determined by the modified Bethesda assay (Nijmegen modification), using congenital FVIII-deficient human plasma, spiked with *Human-cl rhFVIII,* at the following time points:

- At Screening Visit, which will most likely be the same sampling time-point as the completion visit of GENA-05
- Once every 6 months in the course of the follow-up visits
- At study completion
- Any time in the case of a suspicion of inhibitor development.

In case of a positive inhibitor result, an inhibitor retesting, using a second separately drawn sample, should be performed. A FVIII inhibitor is defined as "positive", if the retesting confirms the positive result, otherwise the result is considered as "negative".

Efficacy of prophylactic treatment

The efficacy of *Human-cl rhFVIII* in the prophylactic treatment will be investigated by calculating the frequency of spontaneous break-through bleeds under prophylactic treatment (see Section 7.2.1.2). Study drug consumption data (FVIII IU/kg per month, per year) per patient and in total will be evaluated. The dates and times of study drug infusions, the details of dose(s), and the product batch numbers used for the prophylactic treatment will be documented.

Efficacy of treatment of bleeds

The efficacy of *Human-cl rhFVIII* in the treatment of bleeds will be investigated by using a 4-point ordinal haemostatic efficacy scale (see Section 7.2.1.3). Details of the bleed, the amount of *Human-cl rhFVIII* needed and the number of injections necessary to stop the bleed will be documented.

Efficacy of surgical prophylaxis

In surgical procedures, the following parameters will be documented:

- One overall efficacy assessment (taking into account the intra- and post-operative assessment) after the end of surgical prophylactic treatment phase, agreed upon between the surgeon and the haematologist (see Section 7.2.1.4)
- Average and maximum expected estimated blood loss, compared to the actual estimated blood loss
- Details on surgical procedure (see Section 7.2.1.4): location, severity, type, expected and actual duration
- Pre-, intra-, and post-operative FVIII plasma levels, if appropriate
- Details of administered dose(s) of *Human-cl rhFVIII* given pre-, intra- and/or post-operatively including dates, times and batch numbers
- Details on concomitantly administered drugs, including all blood and blood product transfusions, excluding standard anaesthetic drugs
- Details on all wound haematomas in terms of capturing, analysing, and reporting these,

including any need for surgical evacuation

- Outcome of the intervention, described by means of a brief narrative.

Safety and tolerability

Safety and tolerability will be assessed by monitoring vital signs, standard laboratory parameters, and by monitoring adverse events (AEs).

3.2 Overall Study Design and Plan

This study is designed as a prospective, multicentre, multinational, open-label, non-controlled phase IIIb study in patients who completed GENA-05 in accordance with the study protocol. Around 20-30 centres worldwide are planned to participate in this study.

For each patient, the exposure to *Human-cl rhFVIII*, the efficacy of *Human-cl rhFVIII* in the prevention and the treatment of bleeds, the frequency of break-through bleeds in case of prophylactic treatment, the efficacy in surgical prophylaxis, and the overall safety and tolerability of *Human-cl rhFVIII* will be thoroughly assessed. In the course of the follow-up visits scheduled to be performed every 6 months (± 2 weeks) after the Screening Visit, FVIII inhibitor levels will be assessed for each patient.

The occurrence of AEs and changes in concomitant medication will be checked and documented at each follow-up visit. A patient completes the study by switching to marketed Factor VIII concentrate, the latest 2 years after his screening visit.

In patients undergoing surgical interventions, treatment details will be documented for the pre-, intra-, and post-operative phase, respectively.

This study is planned to start in the 1st quarter 2014 and will be completed by 1st quarter 2016 at the latest.

The tables below summarise the assessments to be performed at the individual visits:

Table 1 Screening Visit (majority of data need to be transferred from GENA-05)

Written informed consent for patients' parents / guardians	✓
Inclusion/exclusion criteria check	✓
Body weight and height measurement	✓
IMP injection after blood sampling (not mandatory)	✓
Diary & IMP instructions	✓

Table 2 Six-Monthly (± 2 weeks) Visits

	Before IMP injection	Time after end of IMP injection§
Body weight measurement	✓	
FVIII inhibitor screen	✓	
Safety lab tests	✓	
IMP injection after blood sampling (not mandatory)	✓	
Vital signs	✓	30-60 minutes (in case IMP is injected)
Physical examination	✓	
Review of diary	✓	
AE monitoring & changes in concomitant medication	<throughout whole period>	

§ Actual time points are to be documented.

Table 3 Bleeding Episodes (BE)

Treatment details	✓
Efficacy assessment at the end of the BE	✓
Type of bleeding (spontaneous, traumatic, post-operative, other)	✓
Site of bleeding	✓
Start date and time of occurrence/of noticing the bleed	✓
Severity of the bleed (minor, moderate to major, or major to life threatening)	✓
Date and time of end of BE	✓

Table 4 Completion Visit

	Before	Time after end of infusion§
Body weight measurement	✓	
Physical examination	✓	
FVIII inhibitor screen	✓	
Safety lab tests	✓	
IMP injection after blood sampling (not mandatory)	✓	
Vital signs	✓	30-60 minutes (in case IMP is injected)
Review of diary	✓	
AE monitoring & changes in concomitant medication	<throughout whole period>	

§ Actual time points are to be documented.

Table 5 Surgery

	within 12 hours before start	within 3 hours before start	Surgery			POP Day 1	any POP Day	last POP Day
			start	intra-op	end			
Body weight	✓							
Estimation blood loss & Duration of surgery	✓							
Details on surgery (location, type, severity, duration)					✓			
Actual blood loss					✓			
Concomitant medications	<---------- throughout whole period ---------- >							
Details study drug injection(s)			( )	( )	( )	( )	( )	( )
Major surgery: FVIII level (mandatory for the first 3 postoperative infusions)*		✓		✓	✓	✓	✓	✓
Minor surgery: FVIII level*		✓		(✓)	(✓)	(✓)	(✓)	(✓)
Efficacy assessment					✓			✓
Safety laboratory tests	✓					✓	(✓)	(✓)
Vital signs	✓			✓		✓		
Wound haematomas						✓	✓	✓
Narrative of outcome								✓
AE monitoring	<---------- throughout whole period ---------- >							

POP = post-operative, ( ) = optional administration; (✓) optional investigation; * <30 minutes prior to and after each study drug administration.

3.3 Discussion of Study Design

3.3.1 Study Design

The present study is an extension study of GENA-05, a study in which the immunogenicity, clinical efficacy, and safety of *Human-cl rhFVIII* in PUPs has been studied.

GENA-15 is a prospective, open-label, uncontrolled, international, multi-centre Phase IIIb study with the objective to collect further long-term data on the immunogenicity, safety and efficacy of *Human-cl rhFVIII.*

Provided the inclusion- and exclusion criteria are met, all subjects wishing to continue treatment with the IMP until *Human-cl rhFVIII* is registered and ready for being launched in the respective country may be included into GENA-15, if they completed GENA-05 in accordance with the study protocol. Thus, individual study participation period varies from country to country, but may not exceed 2 years individual duration from start of screening.

3.3.2 Control Group(s)

Not applicable.

3.3.3 Target Parameters

The following measurements and assessments are requested to be carried out, grouped by the different target parameters:

Immunogenicity

FVIII inhibitor screen

Prophylactic Treatment

Frequency of spontaneous breakthrough bleeds under prophylactic treatment, and in case of surgical prophylaxis

Efficacy

Efficacy assessment at the end of each BE (based on the efficacy scale described in Section 7.2.1.3)

Safety

Vital signs (blood pressure, heart rate, respiratory rate and body temperature)

Safety laboratory parameters (red blood cell [RBC] count, white blood cell [WBC] count, haemoglobin, haematocrit, platelet count, alanine amino transferase [ALT], aspartate transaminase [AST], serum creatinine)

Tolerability (occurrence of any AE will be monitored throughout the study)

4 STUDY POPULATION

4.1 Population Base

The patient population will mainly be young children; however, there was no age limitation in the preceding GENA-05 study.

In total, patients from approximately 20-30 centres from around the world may be enrolled.

4.1.1 Inclusion Criteria

In order to qualify for study enrolment, the following criteria must be fulfilled before study entry:

1. patients who completed GENA-05 in accordance with the study protocol
2. Voluntarily given, fully informed written and signed consent obtained before any study-related procedures are conducted (obtained from the patient's parent/legal guardian)

4.1.2 Exclusion Criteria

Patients will not be included if any of the following exclusion criteria are met:

1. Severe liver or kidney disease (alanine amino transferase (ALT) or aspartate transaminase (AST) levels >5 times of upper limit of normal, creatinine >120 µmol/L);
2. Concomitant treatment with any systemic immunosuppressive drug;
3. Other FVIII concentrate than *Human-cl rhFVIII* was received between completion visit of GENA-05 and start of GENA-15 (except emergency cases).

4.2 Prior and Concomitant Therapy

As this study is conducted in patients who completed the preceding GENA-05 study, patients should not have received any other FVIII concentrates except our IMP for the last 100 EDs.

4.2.1 Permitted Concomitant Therapy

Concomitant administration of therapies not interfering with the objectives of the study is permitted. Details of any concomitant therapies must be recorded in the Case Report Form (CRF).

Vaccinations are permitted prior and during the study, and immunisations should be given as recommended by the country standards. However a subcutaneous administration on a day without FVIII administration is recommended.

Patients may only receive anti-fibrinolytics if this is medically indicated / standard of care, e.g. in the course of tooth extractions or other surgeries.

4.2.2 Forbidden Concomitant Therapy

No FVIII concentrates other than *Human-cl rhFVIII* must be administered (except for emergency situations).

Patients permanently switching to another FVIII product within the study participation period are subsequently withdrawn from the study and a completion visit has to be completed. Patients will be assessed as treatment failures in the efficacy analyses. However, there are exceptions to this rule. Patients will hence not be considered treatment failures in the efficacy analyses, if:

- the use of another FVIII concentrate was due to an emergency case (example: accident requiring treatment with FVIII without patient or intensive care unit [ICU] personnel) having access to Investigational Medicinal Product [IMP])
- the IMP was not available for the patient in time (example: patient experiences a severe bleed but does not have enough product available).

The reason for a patient switching to another FVIII product should be clearly documented in the CRF (and patient diary, if appropriate).

Patients may not receive immuno-modulating drugs (other than anti-retroviral chemotherapy), such as alpha-interferon, prednisone (equivalent to >10 mg/day), or similar drugs.

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Patient Withdrawal

Subjects have the right to withdraw from the study at any time for any reason, without the need to justify. The Investigator also has the right to withdraw subjects in case of AEs, protocol violations, or for administrative reasons. Since an excessive rate of withdrawals can render the study non-interpretable, the unnecessary withdrawal of subjects must be avoided.

The Investigator will obtain all the required withdrawal details and document the reason(s) for discontinuation in the CRF. Should the reason for removal of a subject be an AE, the main specific event or laboratory test will be recorded in the CRF, and the Investigator will make thorough efforts to clearly document the outcome.

4.3.2 Patient Replacement Policy

Patients withdrawn from the study will not be replaced.

4.4 Assignment of Patients to Treatment Groups

As this is a single-arm study, assignment of patients to treatment groups is not necessary.

4.5 Relevant Protocol Deviations

In case of any major protocol deviation or violation, the Investigator and Octapharma will decide on the further participation of the patient in this study after having discussed all relevant aspects.

4.6 Subsequent Therapy

Not applicable.

5 INVESTIGATIONAL MEDICINAL PRODUCT(S)

5.1 Characterisation of Investigational Product(s)

Human-cl rhFVIII is a B-domain deleted, human cell-line derived recombinant FVIII concentrate for intravenous use and will be provided in single use vials containing a nominal potency of 250, 500, 1000 or 2000 IU each of freeze-dried rFVIII concentrate to be reconstituted in 2.5 mL of WFI.

Several batches of the product will be used in the study.

The final product will be released by the responsible Octapharma Quality Control Department, in accordance with a defined final product specification.

5.2 Packaging and Labelling

The open-label study design does not necessitate the blinding of study participants or study site personnel with respect to treatment information. Thus, the IMP will be packed and labelled according to local regulations, together with a pre-filled syringe containing 2.5 mL

WFI (which will be transferred to the product vial), 1 disposable syringe (10 mL), 1 vial adapter, 1 butterfly needle and 2 alcohol swabs.

Details regarding master labelling can be found in Appendix 1.

5.3 Conditions for Storage and Use

The product has to be stored at 2-8°C protected from light. The product must not be frozen.

The Investigators must ensure that the investigational product is stored under appropriate conditions with restricted access. The Investigators will inform the patients' parent(s)/legal guardian(s) of necessary storage conditions once the patients start home treatment.

5.4 Dose and Dosing Schedule

Prophylactic treatment is recommended, but finally, it is the decision of the responsible treating physician whether patients will be treated prophylactically or on-demand. Patients may switch from on-demand to prophylactic treatment, or from prophylactic to on-demand treatment during the course of the study.

Prophylactic Treatment

In case prophylactic treatment is chosen, the patients will be treated with a recommended dose of >20 IU FVIII/kg body weight (BW).

The frequency of treatment will mainly depend on the patient's clinical situation. In cases of inadequate response, *Human-cl rhFVIII* administration frequency or dose adjustments can be considered at Investigator's discretion.

On-demand Treatment

In case of bleeds, the patients can be treated on-demand. The dosage and duration of treatment of spontaneous or traumatic bleeds depend on the location and the extent of bleeding as well as on the clinical situation of the patient. Dosage recommendations are given as follows:

- Minor haemorrhage (superficial muscle or soft tissue and oral bleeds): 20-30 IU FVIII/kg BW to achieve an intended target peak level of about 40% to 60%. Repeat dose every 8-24 hours until BE is resolved.
- Moderate to major haemorrhage (haemorrhage into muscles, into oral cavity; haemarthrosis, known trauma): 30-40 IU FVIII/kg BW to achieve an intended target peak level of about 60% to 80%. Repeat dose every 6-24 hours until BE is resolved.
- Major to life-threatening haemorrhage (intracranial, intra-abdominal, gastro-intestinal or intrathoracic bleeds, central nervous system bleeds, bleeding in retropharyngeal spaces or iliopsoas sheath, eyes/retina, fractures or head trauma): initial dose of 50-80 IU FVIII/kg BW to achieve an intended target peak level of 100% to 120%. Repeat dose of >20 IU FVIII/kg BW every 6-12 hours until BE is resolved.

Surgical Prophylaxis

The dosage and duration of treatment with *Human-cl rhFVIII* will depend on the type of surgery and the patient's individual incremental recovery. Dosage recommendations are given as follows:

- Minor surgeries including tooth extractions: 25-30 IU FVIII/kg BW starting within 3 hours prior to surgery to achieve an intended target peak level of >30%. Repeat one dose every 12-24 hours if needed. Trough levels should be maintained at ≥30%.

- Major surgeries: >50 IU FVIII/kg BW within 3 hours prior to surgery to achieve an intended target peak level of approximately 100%. Repeat if necessary after 6-12 hours initially and for at least 6 to 14 days until healing is complete and recurrence to regular prophylactic treatment is possible. Trough levels should be maintained at >50%.

5.5 Preparation and Method of Administration

Human-cl rhFVIII will be provided in single use vials containing a nominal potency of 250, 500, 1000 or 2000 IU each of freeze-dried rFVIII concentrate to be reconstituted in 2.5 mL of WFI.

Prior to injection, the solution must have reached room temperature, without taking any specific warming-up measures. The preparation should be administered within 3 hours after reconstitution at one single occasion. The solution is a clear or slightly opalescent colourless solution. Solutions that are cloudy or have deposits must not be used. *Human-cl rhFVIII* should be injected intravenously by bolus injection (maximally 4 mL/minute) by using aseptic technique.

5.6 Blinding, Emergency Envelopes and Breaking the Study Blind

Not applicable.

5.7 Treatment Compliance

5.7.1 Drug Dispensing and Accountability

A drug dispensing log will be kept up to date by the Investigator, detailing the dates, batch numbers, and quantities of investigational product dispensed to each patient. The inventory will be available to the Study Monitor in order to verify drug accountability in the course of the study. Patients' parent(s)/legal guardian(s) will be advised to return any empty vials and unused investigational product on the occasion of the study visits.

Any unused investigational product not dispensed, or returned by the patient, will be counted and returned to the Sponsor.

In certain cases, unused supplies might have to be destroyed at the study site. However, this is only applicable after drug accountability has been verified and fully re-conciliated, and after written approval from the Sponsor has been obtained.

The Investigator will ensure that such a disposition does not expose patients to risks linked to the investigational product. The Investigator and the Sponsor will maintain records of any such alternate disposition to permit accurate drug accountability.

5.7.2 Assessment of Treatment Compliance

Patients will usually undergo at-home treatment (treatment will likely be administered by parents/guardians due to the expected young age of the patients or by general practitioners or nurses, if accepted by national regulations). At the first visit, the Investigator will provide a sufficient amount of study medication and a diary to the parents. The Investigator will advise the parents/guardians on how to fill in the diary. The diary will include detailed written instructions for all assessments to be made. Furthermore, the efficacy rating criteria and the criteria for assessing the severity of a bleed will be explained. The Investigator will emphasise the necessity of a careful documentation of all treatment details. The recording of at-home injections will include the date and time, dose, batch number, and reason for

injection (i.e. prophylaxis, BE treatment). IMP is provided with tear-off labels that must be placed in the diary.

In case of treatment of BEs, the patient's parents/guardians will document the site and severity of the bleed, the start and end dates and time, and carry out an efficacy assessment according to the explanation provided in the diary.

Study product administrations that are overseen by the Investigator (e.g. treatment in relation to severe BEs treated at the study site), are to be documented in the patient's journal (by the Investigator), as well as in the patient's diary (by the parents/guardians).

In addition, the patient's parents/guardians will record any concomitant medications taken during the study period in their diaries.

For each follow-up visit at the study site, the parents/guardians must bring all diaries to be reviewed and validated by site personnel.

6 STUDY CONDUCT

6.1 Observations by Visit

6.1.1 Screening (Visit 1)

Parents/guardians have to be informed about the study details and have to give their written informed consent before any investigations and assessments can be performed. The majority of data required are available from the preceding GENA-05 study, and only the following information will be documented/assessed:

- Check of inclusion- and exclusion criteria
- Height
- Body weight

The Investigator will hand out the patient diary and instruct the parent(s)/legal guardian(s) on how to document details of treatment with *Human-cl rhFVIII*, bleeds, AEs and concomitant medication. The parent(s)/legal guardian(s) will receive a sufficient amount of study product for home treatment and will be instructed on how to store and administer it.

6.1.2 Procedures During the Follow-Up Part of the Study

Follow-Up Visits (every 6 months ± 2 weeks):
The patients will visit the study site every 6 months (± 2 weeks). At these visits, blood samples will be obtained for FVIII inhibitor screen (after a wash-out period of at least 2, preferably 3 days after the previous IMP administration). Samples are analysed in the central laboratory. The safety laboratory parameters will be assessed (samples are analysed locally) and vital signs will be measured pre- and – in case IMP was injected – 30-60 minutes post-injection and the patient's BW will be measured. A physical examination is performed.

At these visits, the patient diary will be reviewed, and data are transferred into the CRF. The occurrence of AEs and changes in weight and concomitant medication will be checked and documented.

Surgical Visits:

Study subjects may undergo surgical interventions during the course of the study. Depending on the type of surgery, subjects may be hospitalised or not (in case of certain minor surgeries with low risk of post-operative bleeding) at the discretion of the Investigator. Patient's BW

will be recorded within 12 hour before the start of surgery. Estimations of blood loss and duration of surgery will be recorded. Details of *Human-cl rhFVIII* dosing, concomitant treatment (including need for additional blood transfusions, excluding anaesthetic drugs), AEs (if any) and vital signs will be documented throughout the surgery. Details of surgery, actual blood loss, efficacy assessment, presence of wound haematomas and narratives of outcomes will be recorded after the surgery.

Completion Visit:

For each patient, the study is completed once the IMP is registered and ready for launch in the individual country of study conduct, but latest after 2 years individual study duration - from screening.

At this visit, blood samples will be obtained for FVIII inhibitor screen (after a wash-out period of at least 2, preferably 3 days after the previous IMP administration) and the safety panel. Samples for FVIII inhibitor screen are analysed in the central laboratory.

The vital signs and a physical examination will be performed. The patient's BW will be measured. The occurrence of AEs and changes in concomitant medication are checked and documented.

At these visits, the patient diary will be reviewed, and data are transferred into the CRF.

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The patients may stay in the study until the IMP is registered and ready for launch in the individual country of study conduct, but latest after 2 years individual study duration - from screening.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed when the registration of the IMP is achieved. This study is planned to start in the 1st quarter 2014 and will be completed by 1st quarter 2016 at the latest.

6.2.3 Premature Termination of the Study

Both the Investigator and the Sponsor reserve the right to terminate the study at any time. Should this be necessary, the required procedures will be arranged on an individual basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

7 ASSESSMENTS AND METHODS

7.1 Background / Baseline Information

The majority of required background / baseline information is known from the preceding study GENA-05, and does not need to be documented, again, but will be transferred from the GENA-05 database.

Demographics: date of birth, patient number in GENA-05

After parents (or legal guardians) have given their written informed consent, subjects keep the same unique subject numbers as used in the preceding study GENA-05, except that '*05*' will be replaced by '*15*'.

Medical history: obtained from existing medical charts and by interviewing the parent(s)/legal guardian(s) and by performing a physical examination

7.2 Efficacy/Immunogenicity Assessments

7.2.1 Assessments for Endpoint

7.2.1.1 Immunogenicity

The objective is to investigate the immunogenicity of *Human-cl rhFVIII*.

Inhibitor activity will be determined centrally by the modified Bethesda assay (Nijmegen modification), using congenital FVIII-deficient human plasma spiked with *Human-cl rhFVIII* at the following time points:

- At Screening Visit, which is most likely the same sampling time-point as the completion visit of GENA-05
- Once every 6 months during the open treatment phase
- At study completion
- Any time in the case of a suspicion of inhibitor development.

In case of a positive inhibitor result, an inhibitor re-testing using a second separately drawn sample should be performed centrally. The definitions for thresholds are ≥ 0.6 to < 5 BU for a "low titre" inhibitor and ≥5 BU for a "high-titre" inhibitor.

7.2.1.2 Prophylactic treatment

The following parameters will be documented:

- Dates and times of study product injections
- Details of dose(s) (in IU) and product batch numbers
- Details of BEs (if any) occurring under prophylactic treatment

Study drug consumption data (FVIII IU/kg per month, per year) per patient and in total (for patients on prophylactic treatment) will be evaluated.

Efficacy Assessment of Prophylactic Treatment

The efficacy of *Human-cl rhFVIII* in prophylactic treatment will be evaluated based on the frequency of spontaneous breakthrough bleeds per months under three times weekly or every other day prophylactic treatment and will be calculated and assessed as excellent, good, moderate or poor:

Excellent: Less than 0.75 spontaneous BEs per month

Good: Between 0.75 and 1 spontaneous BEs per month

Moderate: Between more than 1 and 1.5 spontaneous BEs per month

Poor: More than 1.5 spontaneous BEs per month

The time period for prophylactic treatment will comprise the time periods between first prophylactic treatment with *Human-cl rhFVIII* until the administration of the last

prophylactic treatment + 2 days or completion visit whichever comes first) minus time periods from start of a surgery until final assessment of the surgery, and minus time period of on demand treatment, if any.

The frequency of treatment will mainly depend on the patient's clinical situation and may vary from every other day to once weekly injections. In cases of inadequate response, *Human-cl rhFVIII* administration frequency or dose adjustments can be considered at Investigator's discretion.

The number of BEs counted for prophylactic treatment efficacy assessment will comprise all BEs starting during the time periods for prophylactic treatment defined above, i.e. BEs occurring between start of surgery until final assessment of the surgery will not be included in the prophylactic treatment assessment.

7.2.1.3 Bleeding episodes

For all BEs occurring within the study period, the following data will be documented:

- Type of bleeding (spontaneous, traumatic, post-operative, other)
- Site of bleeding
- Start date and time of occurrence/of noticing the bleed
- Severity of the bleed (minor, moderate, major or life threatening, see Section 5.4)
- Date and time of end of BE*
- Efficacy assessment at the end of the BE (definitions see below)
- Details of dose(s) and batch number used to treat BE (in IU)
- Dates and times of study product injections

* If the treatment of a BE in one bleeding site is interrupted for more than 48 hours, two separate BEs will have to be recorded; if another – in addition to the original – bleeding site is affected, the events will be recorded as separate BEs at any time.

All above listed parameters will be documented by the parents/guardians (together with the Investigator in case of on-site treatments) in the patient's diary. Patients experiencing a major or life-threatening BE should preferably be treated at the study site.

After the end of a BE the patient is intended to return to his regular prophylactic treatment regimen.

Efficacy Assessment of Bleeding Episodes

At the end of a BE, the following efficacy assessment will be made by the patient's parent(s)/legal guardian(s) (together with the Investigator in case of on-site treatment):

Excellent: Abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single infusion

Good: Definite pain relief and/or improvement in signs of bleeding within approximately 8 – 12 hours after an infusion requiring up to 2 infusions for complete resolution

Moderate: Probable or slight beneficial effect within approximately 12 hours after the first infusion requiring more than two infusions for complete resolution

None: No improvement within 12 hours, or worsening of symptoms, requiring more than 2 infusions for complete resolution

The assessment will be made at the end of a BE.

7.2.1.4 Surgical Prophylaxis

In case surgical procedures are performed, the following data will be documented:

- Location and type (planned or emergency) of surgery
- Severity of surgery (minor or major, definitions see below)
- Expected duration of surgical procedure
- Actual BW prior to surgery (kg)
- Actual duration of surgical procedure (start and end times, i.e. skin to skin)
- Pre-, intra-, and post-operative FVIII plasma levels (time-points see below)
- Expected and actual blood loss (see below)
- All wound haematomas, incl. capture, analysis, and reporting, noting whether surgical evacuation is required
- Laboratory tests (haematology, chemistry: before and 24 hours after end of surgery)
- Details on concomitantly administered products including any blood/blood product transfusions but *excluding* drugs given for routine anaesthesia
- Details of administered dose(s) of *Human-cl rhFVIII* given pre-, intra- and/or post-operatively (definitions see below) including dates, times, and batch number
- A brief narrative describing the outcome and efficacy of the intervention
- Overall efficacy assessment at the end of surgical prophylaxis by the surgeon and the haematologist (definitions see below)

Classification of Surgeries

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

- Requiring general or spinal anaesthesia
- Requiring opening into the great body cavities
- In the course of which hazards of severe haemorrhage is possible
- Requiring haemostatic therapy for at least 6 days
- 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.

FVIII Plasma Level

FVIII plasma level (both assays, local and central lab) will be documented at the following time-points:

- Immediately (≤30 minutes) before and after pre-operative injection of study drug
- Immediately (≤30 minutes) before and after each intra-operative bolus dose (if any); not mandatory for minor BEs
- Immediately (≤30 minutes) before and after each post-operative dose (if any); in case of major surgery: mandatory for the first 3 post-operative doses

Continuous infusion is not allowed in this study, only bolus injections are permitted.

Estimation of Blood-Loss

Prior to surgery, the surgeon will provide written estimates of the following:

Volume (mL) of *average* expected blood loss for the planned surgical procedure, as it would be expected for the same procedure in a patient with normal haemostasis, of the same sex, age, and stature.

Volume (mL) of *maximal* expected blood loss for the planned surgical procedure as it would be expected for the same procedure in a patient with normal haemostasis, of the same sex, age, and stature.

Following the surgery, the **actual** blood loss will be estimated by the surgeon.

Definitions of Pre-, Intra-, and Post-Operative Doses

A pre-operative administration is defined as any dose of *Human-cl rhFVIII* applied within 3 hours prior to surgery start.

An intra-operative administration is defined as any injection of *Human-cl rhFVIII* applied during surgery.

A post-operative administration is defined as any dose of *Human-cl rhFVIII* applied after the end of the surgery ("end of surgery" is defined as "last suture"), for at least 2 days (minor surgeries), or for at least 6 to 14 days (major surgeries), respectively, until healing is achieved and recurrence to the regular prophylactic treatment regimen.

Efficacy Assessment of Surgical Prophylaxis

Efficacy will be assessed (1) at the end of surgery by the surgeon, and (2) post-operatively by the haematologist, and finally (3) overall by an agreed upon assessment from the surgeon and the haematologist using the following scales:

Intra-operatively (at the end of the surgery [= after last suture]):

- Excellent: Intra-operative blood loss was lower than or equal to the average expected blood loss compared with the same type of procedure performed in a patient with normal haemostasis and of the same sex, age, and stature.
- Good: Intra-operative blood loss was higher than average expected blood loss but lower or equal to the maximal expected blood loss compared with the same type of procedure in a patient with normal haemostasis.
- Moderate: Intra-operative blood loss was higher than maximal expected blood loss compared with the same type of procedure performed in a patient with normal haemostasis, but haemostasis was controlled.
- None: Haemostasis was uncontrolled necessitating a change in clotting factor replacement regimen.

Post-operatively:

- *Excellent*: No post-operative bleeding or oozing that was not due to complications of surgery. All post-operative bleeding (due to complications of surgery) was controlled with *Human-cl rhFVIII*, as anticipated for the type of procedure.
- *Good*: No post-operative bleeding or oozing that was not due to complications of surgery. Control of post-operative bleeding due to complications of surgery required increased dosing with *Human-cl rhFVIII* or additional infusions, not originally anticipated for the type of procedure.
- *Moderate*: Some post-operative bleeding and oozing that was not due to complications of surgery; control of post-operative bleeding required increased dosing with *Human-cl rhFVIII* or additional infusions, not originally anticipated for the type of procedure.
- *None*: Extensive uncontrolled post-operative bleeding and oozing. Control of post-operative bleeding required use of an alternate FVIII concentrate.

An overall efficacy assessment taking both the intra- and post-operative assessment into account will be done by the surgeon and the haematologist.

The conclusion of the post-operative phase of a major surgery is defined as follows: date of discharge, or at least post-operative Day 6, whichever occurs later.

At the end of a surgical prophylactic treatment period the patient is intended to return to his regular prophylactic treatment regimen.

7.3 Safety Assessments

7.3.1 Adverse Events

All AEs and SAEs will be monitored and recorded throughout the study.

7.3.1.1 Definitions

Adverse event (AE): An AE is any untoward medical occurrence in a study patient receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

Adverse drug reaction (ADR): An ADR is any noxious and unintended response to an IMP related to any dose. The phrase “response to an IMP” means that a causal relationship between the IMP and an AE carries at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Other significant AEs: Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction or significant additional concomitant therapy.

Withdrawal due to AE/ADR: Is a patient whose treatment with IMP is discontinued because of an AE or ADR. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the patient is stable. All follow-up information collected will be made available to the Sponsor.

7.3.1.2 Collection

The condition of the patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard non-leading question such as "How have you been since the last visit / during the previous study period?" In addition, the patient diaries (if applicable) will be checked by the Investigator for any documented event.

Any AE or ADR which occurs during the study will be noted in detail on the appropriate pages of the CRF. If the patient reports several signs or symptoms, which represent a single syndrome or diagnosis, the latter should be recorded in the CRF. The Investigator responsible will grade the severity of all AEs or ADRs (mild, moderate or severe), the seriousness (non-serious or serious) and causality, as defined below (Sections 7.3.1.3, 7.3.1.4 and 7.3.2). The Sponsor is responsible to assess the expectedness of each ADR (expected or unexpected), as defined below (Section 7.3.1.4).

In the event of clinically significant abnormal laboratory findings, the tests will be repeated and followed-up until they have returned to normal and/or an adequate explanation is available.

Diseases, signs and symptoms and/or laboratory abnormalities already existing before the first administration of IMP are not considered as AEs when observed at a later stage unless they represent an exacerbation in intensity or frequency (worsening).

The Investigator responsible should always provide detailed information concerning any abnormalities and the nature of, and reasons for any necessary action(s), as well as any other observations or comments, which are useful for the interpretation and understanding of the patients' AEs or ADRs.

7.3.1.3 Severity

The intensity/severity of all AEs will be graded as follows:

- mild: an AE, usually transient, which causes discomfort but does not interfere with the patient's routine activities;
- moderate: an AE which is sufficiently discomforting to interfere with the patient's routine activities;
- severe: an AE which is incapacitating and prevents the pursuit of the patient's routine activities.

Grading of an AE is up to the medical judgement of the Investigator and will be decided on a case by case basis.

7.3.1.4 Causality

The relationship of AEs to the administered IMP will be assessed by the Investigator responsible:

- probable: reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the patient's clinical state.

- possible: reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.
- unlikely: reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.
- not related (unrelated): events for which sufficient information exists to conclude that the aetiology is unrelated to the IMP.
- unclassified: reports which for one reason or another are not yet assessable, e.g. because of outstanding information (can only be a temporary assessment).

Classification of ADRs:

ADRs will be classified by the Sponsor as either expected or unexpected:

- expected: an AE that is listed in the "Reference Safety Information" of the current edition of the Investigator's Brochure.
- unexpected: an AE that is not listed in the current edition of the Investigator's Brochure, or that differs because of greater severity or greater specificity.

7.3.1.5 Outcome

The outcome of all reported AEs has to be documented as follows:

1. recovered, resolved
2. recovering, resolving
3. not recovered, not resolved
4. recovered, resolved with sequelae
5. fatal
6. unknown

NOTE: A patient's **death** *per se* is not an event, but an outcome. The event which resulted into patient's death must be fully documented and reported, even in case the death occurs within 4 weeks after IMP treatment end, and without respect of being considered treatment-related or not.

7.3.1.6 Action(s) taken

AEs requiring action or therapy must be treated with recognised standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

The action taken by the Investigator must be documented:

In general

- none

- medication (other than IMP) or other (e.g., physical) therapy started
- test performed
- other (to be specified)

On IMP

- none
- product withdrawn
- dose reduced
- dose increased

The responsible Investigator will follow-up each AE until it is resolved or until the medical condition of the patient is stable, and all relevant follow-up information will be reported to the Sponsor.

7.3.2 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is another important medical event.

In addition, each FVIII inhibitor development is regarded as an SAE.

NOTE: The term "life-threatening" refers to an event in which the patient was — in the view of the reporting Investigator — at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgment should be exercised in deciding whether an AE/reaction is serious in other situations: Important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definitions above, should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent should be reported as SAE. A suspected virus transmission means that virus antigen has been detected in the patient. A passive transmission of antibodies alone does not constitute a suspected virus transmission.

SAE reporting timelines

All SAEs, whether suspected to be related to study treatment or not, are to be reported by telephone, fax or e-mail immediately to the Clinical Project Manager or designee.

Contact details for SAEs reporting are available on the “Serious Adverse Event Report” and below.

An Octapharma "Serious Adverse Event Report" must be completed and submitted within 24 hours after recognition of the event.

All SAEs should additionally be reported to:

Waiver from SAE reporting requirement:

The following SAEs do not require reporting in expedited manner:

- Hospitalisation for the treatment of a (disease-related) BE assessed as unrelated to IMP treatment.

These exceptions/waivers include surgeries that are elective or planned, and prolongation of the existing hospitalisations due to economic or social reasons, but not medical reasons. These should not be considered as SAEs.

7.3.3 Laboratory Safety Tests

Blood Sampling

The *actual* date and time of any blood sampling must be recorded in the CRF, on the label of the laboratory tubes and on the corresponding laboratory shipment forms.

If several blood samples have to be taken at one time point, the blood sampling will be done in the following sequence:

1. Haematology: RBC count, WBC count, haemoglobin, haematocrit, platelet count (EDTA blood)
2. Coagulation: FVIII plasma level and FVIII inhibitor control (citrated plasma)
3. Biochemistry: ALT, AST, serum creatinine (serum)

It is essential that blood sampling after the injection of *Human-cl rhFVIII* is done from the other arm.

Blood samples taken for citrate plasma will be centrifuged after collection for 15 to 20 minutes at 1500 to 2000 g (about 3000 rpm). Aliquots of the supernatant are subsequently transferred into the tubes provided by the central laboratory (pre-labelled with date and time point of sampling, type of sample, patient identification and study number) and stored, respectively shipped under adequate conditions.

EDTA Blood

A 1 mL sample (or less, as required by the local laboratory) of EDTA blood will be collected for the measurement of haematology parameters (RBC count, WBC count, haemoglobin, haematocrit, platelet count). All haematology tests are to be done at the local laboratory.

Citrated Plasma

For the analysis of FVIII (if applicable) and inhibitor screen, both performed in the central laboratory in the US, citrated blood will be collected. After collection and centrifugation, the

plasma will be aliquoted into cryo-resistant tubes. Samples will be stored at ≤-70°C and shipped to the central laboratory on dry-ice.

For analysis performed locally, e.g. at screening and pre-, intra, and post-surgery, citrated blood as required by the local laboratory will be collected and processed in accordance with local requirements.

Serum

For the determination of clinical chemistry (ALT, AST, serum creatinine) a blood sample of about 0.5 mL (or less, as required by the local laboratory) will be collected. All tests are to be done at the local laboratory.

The "Ethical Considerations for Clinical Trials on Medicinal Products conducted with the Paediatric Population" (6) are followed during the conduct of GENA-15. The Committee recommends the below blood volume limits for sampling:

Per individual, the trial-related blood loss should not exceed 3 % of the total blood volume during a period of four weeks, and should not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90 ml/kg body weight; 3% is 2.4 ml blood per kg body weight.

Time-points and required blood / plasma volume needed for laboratory parameters are estimated as follows (please note that the exact amount needed for the analysis performed in the central laboratory can be found in the laboratory manual, only):

Table 6 Time-Points and Approximate Blood Volume for Laboratory Parameters

	Screening	**Follow-Up**		**Surgery**
	Results from GENA-05 completion visit are transferred – no additional blood sampling	6-Months Visits (+ 2 weeks)	Completion Visit	(Pre-, intra- and post-surgery)
FVIII inhibitor screen		1.4 mL/0.7 mL	1.4 mL/0.7 mL	
Haematology		~1 mL EDTA blood	~1 mL EDTA blood	~1 mL EDTA blood
Clinical chemistry		~0.5 mL serum	~0.5 mL serum	~0.5 mL serum
FVIII:C		1.4 mL/0.7 mL	1.4 mL/0.7 mL	1.4 mL/0.7 mL

All treatment-emergent rise in AST or ALT to >3 x ULN will be followed by assessing liver function tests until their return to normal; or (in case of *a priori* increased values) until their return to the individual's baseline; or until a definite diagnosis is determined.

If the abnormal values persist for more than 1 week, viral serology (hepatitis B virus, hepatitis C virus, and/or others) and PCR testing will be performed by the local laboratory. In addition, PCR testing of the corresponding batches will be performed by the central lab.

The Investigator must assess the clinical significance of abnormal laboratory values outside the normal range as specified by the reference laboratory. Any clinically significant abnormalities should be fully investigated.

Only laboratory abnormalities that have been rated as being clinically significant will be documented as AEs/ADRs. Clinically significant is defined as any laboratory abnormality that the Investigator feels is of clinical concern, and/or requires medical intervention and/or follow-up. Additional tests and other evaluations required to establish the significance, or aetiology of an abnormal result or to monitor the course of an AE should be obtained if clinically indicated. Any abnormal laboratory value that persists should be followed until resolution or for 14 days after the final study visit, whichever occurs first. Preferably, clinically significant lab abnormalities should be medically diagnosed and entered as a diagnosis into the AE form, if not already present at baseline.

The following table summarises all test parameters and the laboratory responsible for analysis:

Table 7 Test Parameters and Laboratories

Test	Material needed	Responsible laboratory
FVIII:C*‡ (one-stage and chromogenic assay)	Citrated plasma	LabCorp Clinical Trials Laboratory Services 8490 Upland Dr, Ste. 100 Englewood, CO 80112, USA
Inhibitors to FVIII (modified Bethesda assay - Nijmegen modification)	Citrated plasma	
Haematology	EDTA blood	Local laboratory
Clinical chemistry	Serum	Local laboratory
PCR testing of *Human-cl rhFVIII* batches†	Human-cl rhFVIII	Octapharma AB Elersvägen 40 11275 Stockholm, Sweden

* Performed locally when required, e.g. pre-, intra- and post-surgery.
† Performed if abnormal AST or ALT values persist for more than 1 week.

All remaining serum and plasma volumes will be labelled and stored as retention samples at the central laboratory for at least 2 years after the completion of the study and until Octapharma's written authorisation to destroy these samples.

7.3.4 Vital Signs and Physical Examination

Vital signs (blood pressure, heart rate, respiratory rate, body temperature) will be assessed at the following time-points: at screening (results are to be transferred from GENA-05's completion visit), prior and – in case IMP was injected – 30-60 minutes after the end of the injection at 6-monthly (± 2 weeks) visits, and prior and – in case IMP was injected – 30-60 minutes after the end of the injection at the completion visit. During surgical procedures vital signs will be assessed before, during and at the first post-operative day.

A physical examination needs to be performed at screening (results are to be transferred from GENA-05's completion visit), once every 6 months and at study completion.

7.3.5 Other Relevant Safety Information

Post study related safety reports:

Any ADR (i.e., any AE with a suspected causal relationship to the IMP) that occurs after the completion of the study should be reported by the Investigator. The usual procedure for reporting post-marketing safety information should be followed, but relation to the clinical study should be stated on the report.

If a patient dies within 4 weeks after the last IMP administration, this should be reported as well, without being considered treatment-related or not.

Overdose, interaction, abuse, misuse, medication error and lack of efficacy:

The following safety relevant information should be reported as an AE or, if the reaction fulfils one of the criteria for seriousness, as a SAE.

Drug overdose:

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than that specified in the protocol, and higher than the known therapeutic dose and of clinical relevance. The reaction must be clearly identified as an overdose.

Interaction:

A drug interaction is a situation in which a substance/medicinal product affects the activity of an IMP, i.e., the effects are increased or decreased, or they produce an effect that none of the products exhibits on its own. The reaction must be clearly identified as drug interaction.

Misuse:

Misuse is the deliberate administration or use of the medicinal product outside its described indication or outside the current state of the art medical practice (off-label-use). The reaction must be clearly identified as misuse.

Medication error:

Medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, instructions for use/labelling. The reaction must be clearly identified as a medication error.

7.4 Appropriateness of Measurements

All measurements used for the assessment of the immunogenicity, safety, and efficacy of *Human-cl rhFVIII* are in compliance with the requirements set up in the CHMP "Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products" (EMA/CHMP/BPWP/144533/2009) (5).

All FVIII inhibitor and FVIII plasma level samples obtained in the course of this study will be evaluated by an accredited central laboratory using validated methods and assays.

If clinically indicated, FVIII and inhibitor testing can additionally be performed in the local laboratory. The results obtained locally will be recorded in the CRFs.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all the information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (e.g., case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the Investigator will indicate in the source record(s) that the patient participates in this study.

All data entered in the CRF must be supported by source data in the patient records with the exceptions listed in Section 8.1.2.

The Investigator will permit study-related monitoring, audit(s), Independent Ethics Committee [IEC]/ Institutional Review Board [IRB] review(s) and regulatory inspection(s), by providing direct access to source data/records.

The Investigator may authorise site staff (e.g., sub-Investigators, nurses) to enter study data into the CRF. This must be documented in the "Delegation of Authority Log", filled in and signed by the Investigator responsible.

8.1.2 Case Report Forms

For each patient enrolled, a CRF will be completed and signed by the Investigator or an authorised Co-Investigator. All forms will be filled out using an indelible pen, and must be legible.

8.1.3 Changes to Case Report Form Data

Errors occurring in CRFs will be crossed out without obscuring the original entry, the correction will be written alongside the initial entry, and the change will be initialled and dated by the Investigator or authorised study site personnel. When changes to CRF data are necessary following removal of the original CRF from the study site, any such changes will be documented on data clarification / resolution forms, which will be submitted to the Investigator for signature.

If reason for the change is not obvious, then a reason should be given. The Principal Investigator must, as a minimum, sign the final CRF page to attest the accuracy and completeness of all the data. Once the data have been entered onto the database, they will be checked and any discrepancies will be raised and returned to the Investigator for resolution. Data will be monitored and tabulated in accordance with the Data Management Plan.

8.2 Information of Investigators

An Investigator's Brochure will be handed out to the Investigator before the start of the study. This Brochure contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The Investigator's Brochure will be updated by the Sponsor at regular intervals and in case new information concerning the IMP becomes available.

The Investigators will be informed about the methods for rating relevant study outcomes and for completing CRFs in order to reduce discrepancies between participating Investigators and study sites.

The Investigator will be kept informed of important data that relate to the safe use of the IMP as the study proceeds.

8.3 Responsibilities

The Co-ordinating Investigator of this study is Dr Raina J Liesner, Great Ormond Street Hospital for Children, NHS Trust, Haemophilia Centre, Great Ormond Street, London WC1N 3JH, United Kingdom.

The central laboratory for all coagulation parameters and inhibitor testing is LabCorp Clinical Trials, Laboratory Services, 8490 Upland Dr, Ste. 100, Englewood, CO 80112, USA.

Statistical advice during the planning phase, study data management and statistics of the study will be delegated under an agreement of transfer of responsibilities to GASD mbH, Am Konvent 8-10, 41460 Neuss, Germany.

All Octapharma SOPs, procedures and policies have to be met by external parties (Contract Research Organisations [CROs] and central laboratories), discrepancies or exceptions are to be approved by Octapharma.

All parties involved in the study are responsible to comply with local and international obligations, regulatory requirements and duties in accordance with local laws, using the principles of good clinical practice (GCP) and good laboratory practice (GLP) guidelines, SOPs and complying with all other applicable regulations.

8.4 Investigator's Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (e.g., copies of the protocol, study approval letters, all original informed consent forms, site copies of all CRFs, drug dispensing and accountability logs, correspondence pertaining to the study, etc.) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential patient identification code list, which provides the unique link between named source records and CRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the Investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the patient's confidentiality is maintained. This is particularly important when CRFs are illegible or when errors in data transcription are encountered. In case of particular issues or governmental queries, 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.

8.6 Independent Data Monitoring Committee

GENA-05 is monitored by an Independent Data Monitoring Committee (IDMC). GENA-15 is an extension study of GENA-05and is not monitored by the IDMC.

9 STATISTICAL METHODS AND SAMPLE SIZE

The statistical analysis will be delegated under an agreement of transfer of responsibilities to an external CRO. All Octapharma procedures and policies have to be met by this CRO. Discrepancies or exceptions are to be approved by the Sponsor's Manager of Biometrics.

9.1 Determination of Sample Size

No inferential analysis involving formal testing is planned in this non-controlled extension study. Consequently, no formal sample size estimation was performed.

9.2 Statistical Analysis

A formal statistical analysis plan (SAP) describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to the start of the study.

The statistical analysis of the endpoints is to be understood in the exploratory sense. No confirmatory hypothesis testing is planned.

9.2.1 Population for Analysis

For the analysis of this study, the following populations will be considered:

- Safety analysis population: All subjects who received at least one dose of *Human-cl rhFVIII*;
- Intent to Treat (ITT) analysis population: All subjects in the safety analysis population for whom any data was collected post treatment with *Human-cl rhFVIII*;
- Efficacy: Per Protocol (PP) analysis population: All subjects in the ITT analysis population who completed the trial without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the efficacy results.
  Especially the following subjects will be excluded from this population:
  - Subjects who fulfil the following exclusion criteria:
    - severe liver or kidney disease (ALT and AST levels >5 times of ULN, creatinine >120 µmol/L),
    - concomitant treatment with any systemic immunosuppressive drug
    - subjects who use concomitant medication that may confound study results, like e.g. alpha-interferon or prednisone
    - other FVIII concentrate than *Human-cl rhFVIII* was received between completion visit of GENA-05 and start of GENA-15 (except emergency cases)
  - Subjects with significant non-compliances with the protocol such as non-compliance to complete the diary in a proper manner or more than 30% of haemostatic efficacy assessments missing.
  - Subjects with dosing or treatment errors like e.g. the use of other FVIII products (except for emergencies as mentioned above) or several *unexplained* and significant deviations from the recommended dose regimen.
- <u>Population of subjects on prophylactic treatment schedule (PROPH):</u> All subjects in the ITT population who have at least one prophylactic treatment
- <u>Per-protocol population of subjects on prophylactic treatment schedules (PROPH-PP):</u> All subjects in the PP population who have no significant dosing or treatment errors, like e.g. unexplained interruptions of the prophylaxis with *Human-cl rhFVIII*
- <u>Population of bleedings (BLEED):</u> All documented bleeds - except those occurring during and after surgery - of subjects in the ITT population for which
  - any amount of treatment with *Human-cl rhFVIII* is documented and which
  - start between first BE treated with *Human-cl rhFVIII* and the completion visit.

- Population of bleedings per protocol (BLEED-PP): All documented bleeds in the BLEED population of subjects in the PP population.
- Surgery population (SURG): All documented surgical interventions of subjects in the ITT population for which
  - any amount of *Human-cl rhFVIII* prior to, during or after the surgery is documented and
  - no other FVIII concentrate is documented within 24 hours prior to surgery.
- Surgery per-protocol population (SURG-PP): All documented surgical interventions of subjects in the PP population for which
  - any amount of *Human-cl rhFVIII* prior to, during or after the surgery is documented and
  - no other FVIII concentrate is documented within 72 hours prior to, during or after the surgery (until resuming regular prophylactic treatment or until discharge from hospital in case of a subject with on-demand treatment).

The subject disposition, i.e. the identification of significant violations to consider for the PP populations and the assignment of each subject, bleeding and surgery to these analysis populations, will be the joined decision of the trial statistician and the responsible medical expert prior to database lock.

The ITT population is considered to be the most relevant for analysis of immunogenicity data; the PROPH population is considered to be the most relevant for analysis of efficacy data on prophylaxis; the BLEED population is considered to be the most relevant for analysis of efficacy data on bleedings and the SURG population is considered to be the most relevant for analysis of efficacy data on surgeries. To evaluate the robustness of the study results, efficacy analyses will also be done on basis of the respective PP population.

9.2.2 Efficacy Analysis Plan

Efficacy will be evaluated by descriptive statistics.

- On bleeding rates (efficacy of prophylaxis) overall and by intensity of prophylaxis
- On efficacy assessments per bleed, basic bleed characteristics including severity, site and type
- On efficacy assessments per surgery

The frequency of bleeds, the number of infusions needed to treat a BE, the number of EDs, and study drug consumption data (FVIII IU/kg per infusion, per BE, per month, per year) per patient and in total will be evaluated. Furthermore, increased and decreased doses of *Human-cl rhFVIII* used to treat individual BEs (frequency and relative magnitude of dose changes) will be evaluated, as well as changes in the doses per infusion and changes in the total dose used to treat subsequent BEs of the same type (e.g. elbow, knee, etc.) in the same patient (frequency and relative magnitude of dose changes).

9.2.3 Safety Analysis Plan

All AEs and any changes in physical examination findings during study occurring after initiation of study treatments (including events likely to be related to the underlying disease, or a concomitant illness or medication or clinical significant abnormalities in laboratory parameters or vital signs) will be displayed in summary tables, listings and figures.

Incidences of AEs will be given as numbers and percentages of patients and infusions with:

- Any AE.
- Any serious AE.
- Any AE probably or possibly related to the trial drug.
- Any AE that begins within 24 hours of the end of an infusion.
- Any severe AE.
- Any withdrawal due to AE.
- Any AE by MedDRA preferred term.
- Any AE by MedDRA System Organ Class (SOC).

Summary tables for AEs will be given by SOC and preferred term. Additionally, AEs will be summarised by severity and relationship to study treatment. These summary tables will feature total counts and counts by age group, sex, prior EDs to *Human-cl rhFVIII* (including EDs within GENA-05) and total amount of *Human-cl rhFVIII* (including amount used within GENA-05) used prior to the AE to evaluate the need of further investigation of any apparent pattern or trend in AE rates.

The MedDRA coded terms and the corresponding original (verbatim) terms used by the Investigator will be listed.

Vital signs

Blood pressure (systolic/diastolic), heart rate, respiratory rate and body temperature will be tabulated, and the sample characteristics will be presented by time point.

Routine laboratory data

Routine laboratory parameters (haematology, clinical chemistry) will be listed for all patients, using indicators for values outside the associated reference ranges. Changes from baseline (screening) will be provided where appropriate.

9.2.4 Handling of Missing Data

In general, missing data will not be imputed: calculations pertaining to person-year computations will be based on observed values only. Only in case of missing BW, the last available weight measurement will be used for calculating the dose per kg bodyweight (last observation carried forward).

9.3 Interim Analysis

No interim analysis is planned.

10 ETHICAL / REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical / Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an IEC/IRB and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP regulations and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (e.g. CRO) as required by national law.

10.2 Approval of Study Documents

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 Investigator to the appropriate IEC/IRB and the Regulatory Authority. The study approval letter must be available before any patient is exposed to a study-related procedure.

The Sponsor, the Investigator and any third party (e.g., CRO) involved in obtaining approval, must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 Patient Information and Informed Consent

The investigator will obtain a freely given written consent from each patient/parent/legal guardian after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspect of the study which is relevant to the subject's decision to participate. The informed consent form must be signed, with name and date noted by the patient/parent/legal guardian, before the patient is exposed to any study-related procedure, including screening tests for eligibility.

For patients not qualified to give legal consent, written consent must be obtained from the legal parent or guardian. If children are old enough to understand the risks and benefits of the study, they should also be informed and provide their written consent.

The investigator will explain that the patient/parent/legal guardian are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for the patient's further care and without the need to justify. The investigator will complete the informed consent section of the CRF for each subject enrolled.

Each patient/parent/legal guardian will be informed that the patient's 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.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator (co-ordinating Investigator in multi-centre studies) and the Sponsor prior to its implementation. Any such amendments will be submitted to the IEC(s)/IRB) and/or competent authority responsible as required by applicable regulations. IEC(s)/IRB approval will at a minimum be requested for any change to this protocol which could affect the safety of the patients, the objective/design of the study, any increase in dosage or duration of exposure to the IMP an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patients´ Data

The Investigator 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 number. Documents not for submission to the Sponsor, i.e., the confidential patient identification code list, original consent forms and source records will be maintained by the Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all CRF entries compared to source data. The Investigator will co-operate with the monitor to ensure that any discrepancies identified are resolved.

Monitoring frequency will depend on study progress.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the CRFs, including all laboratory results.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and effectiveness of the IMP have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines and Sponsor's SOPs) will be prepared by the Sponsor after the completion of the study. The co-ordinating Investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is envisaged by an Investigator, the Investigator 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 Investigator.

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

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with the IMP or the participation in the study, Octapharma will contract insurance in accordance with local regulations.

The Investigator is responsible for dispensing the IMP according to this protocol, and for its secure storage and safe handling throughout the study.

14 REFERENCES

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