CLINICAL STUDY PROTOCOL

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

Investigational Product:	Human-cl rhFVIII
Indication:	Severe haemophilia A
Study Design:	Prospective, open-label, multicentre study
Sponsor:	**Octapharma AG** Seidenstrasse 2, 8853 Lachen, Switzerland
Study Number:	GENA-21b
IND Number:	BB-IND 13722
EudraCT Number:	2014-002986-30
Development Phase:	3b
Clinical Start:	2nd Quarter 2015
Planned Clinical End:	3rd Quarter 2018 4th Quarter 2020 (for "Sub-Study Extension Phase" in Japan)
Date of Protocol: Original Protocol Version 01 Amended Protocol Version 02 Amended Protocol Version 03 Amended Protocol Version 04 Amended Protocol Version 05 Amended Protocol Version 06 Amended Protocol Version 07 Amended Protocol Version 08 Amended Protocol Version 09 Amended Protocol Version 10	 July 30, 2014 March 30, 2015 (France only) June 23, 2015 (all countries except France) June 23, 2015 (France only) October 26, 2015 April 4, 2016 (Japan only) May 19, 2016 (Japan only) February 15, 2017 (Japan only) June 7, 2017 (Japan only) July 24, 2019 (Japan only)
Version:	10
Co-ordinating Investigators:	[redacted]

STUDY OUTLINE

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

Title of Study: Prospective, open-label, multicentre phase 3b study to assess the efficacy and safety of personalized prophylaxis with *Human-cl rhFVIII* in previously treated adult patients with severe haemophilia A	
Indication: Haemophilia A	
Number of Study Centre(s): Approximately 30 centres worldwide	
Study Duration: 2nd Quarter 2015 to 3rd Quarter 2018 2nd Quarter 2017 to 4th Quarter 2020 for "Sub-Study Extension Phase" in Japan	**Development Phase:** 3b

Objectives

Primary Objective

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

Secondary Objectives

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

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

Additional Objectives

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

Objectives of the "Sub-Study Extension Phase" to GENA-21b (Japan)

1. To investigate the long-term safety of *Human-cl rhFVIII* in patients with severe haemophilia A who participated in the GENA-21b study
2. To assess the long-term efficacy of *Human-cl rhFVIII* during prophylactic treatment (based on the frequency of total and spontaneous break-through bleeds)
3. To assess the efficacy of *Human-cl rhFVIII* during treatment of bleeding episodes (BEs)
4. To assess the efficacy of *Human-cl rhFVIII* in surgical prophylaxis

Study Design: Prospective, open-label, multicentre phase 3b study

Number of Patients: Approximately 55 subjects (50 evaluable) of which the patients recruited in Japan (approx. 10) will continue in the "Sub-Study Extension Phase"

Patient Selection Criteria

Inclusion Criteria

(a) Severe haemophilia A (FVIII:C < 1%) according to medical history
(b) Male patients ≥ 18 years of age
(c) Previous treatment with any FVIII product(s) (regular prophylaxis with good compliance or on-demand treatment) for at least 150 EDs

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

(d) Good documentation regarding dosing and bleeding frequency in the 6 months preceding study start
(e) Immunocompetence (CD4+ count > 200/µL)
(f) Freely given written informed consent

Exclusion Criteria

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

Patient Selection Criteria for "Sub-Study Extension Phase" (Japan)

Inclusion criteria:

a) Patients who completed the GENA-21b study with 6 months of prophylactic treatment in Treatment Phase II
b) Voluntarily given, fully informed written and signed consent obtained before any "Sub-Study Extension Phase"-related procedures are conducted

Exclusion criteria:

a) Other FVIII product than *Human-cl rhFVIII* was received between completion visit of GENA-21b study and start of "Sub-Study Extension Phase" (except emergency cases).

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

IMP and Mode of Administration

Human-cl rhFVIII is a human cell line derived recombinant FVIII concentrate for intravenous use. Vials contain either 250, 500, 1000, 2000, 2500, 3000, or 4000 international units (IU) of freeze-dried FVIII concentrate, each to be reconstituted in 2.5 mL water for injections. *Human-cl rhFVIII* should be injected intravenously by bolus injection at a maximum rate of 4 mL/min. Continuous infusion is prohibited.

Dosing of the IMP

Initial PK Evaluation (72 hours):

60 ± 5 IU FVIII/kg, according to labelled potency

Prophylactic Treatment—Phase I (1–3 months):

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

The maximum dose for a single infusion in Prophylaxis Treatment Phase I is 45 IU/kg BW.

Prophylactic Treatment—Phase II (6 months):

Patients will be treated prophylactically for 6 months. Prophylactic doses and dosing intervals will be recommended by the Sponsor for each patient based on the analysis of individual PK data obtained at the Initial PK Visit with the one-stage assay. The final decision on the prophylactic scheme will be taken by the investigator after consultation with the patient and Sponsor.

Based on an appropriate PK model, various dosing intervals (usually 12-hour intervals) and corresponding doses (in IU/kg) will be calculated, which hypothetically lead to FVIII:C plasma concentrations of at least 0.01 IU/mL at the end of the respective injection interval.

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

The goal is to use the maximum regular prophylactic dosing interval that can be achieved with a maximum dose of not more than 65 IU/kg and that maintains a trough level of ≥ 0.01 IU/mL.

This recommendation may change in certain situations. For example,

- If the maximum calculated dosing interval is ≤ 2.5 days, the recommendation may be to continue with the dose and dosing interval as used in Prophylactic Treatment—Phase I, provided that this treatment scheme was considered effective by both the treating physician and the patient.
- If the maximum calculated dosing interval is > 3.5 days and the dose > 65 IU/kg, the recommendation may be to reduce the dosing interval by 0.5 days and use the corresponding lower dose.
- If the maximum calculated dosing interval is ≥ 4.5 days, the recommendation may be to reduce the dosing interval by 0.5 days and use the corresponding dose.

In general, the recommendation will take into account both the interpretation of the PK data as well as practical and economic aspects (i.e., consumption of FVIII). The final decision on the prophylactic scheme will be taken by the investigator after consultation with the patient and Sponsor.

At the 4-Month Visit in Prophylactic Treatment—Phase II, the dose per injection for the remainder of the study may be reduced provided that FVIII:C trough levels (one-stage assay) obtained at the 2-Month Visit were ≥ 0.01 IU/mL and the patient has not experienced any spontaneous bleed up to the 4-Month Visit.

In case of unacceptable frequent and/or severe spontaneous breakthrough bleedings, the dose should be increased by approximately 5 IU/kg (depending on the entire content of vial(s) that needs to be reconstituted additionally). However, the maximum dose should not exceed 65 IU/kg. If, after a dose increase, patients still experience unacceptable bleeding episodes, the dosing interval should be shortened.

Treatment of Bleeding Episodes

The dosage and duration of treatment of spontaneous or traumatic breakthrough bleeding episodes (BEs) will depend on the location and extent of bleeding and on the clinical situation of the patient.

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

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.

"Sub-Study Extension Phase" to GENA-21b (Japan)

Patients will continue to be treated prophylactically after the completion of 6 months in Treatment-Phase II in GENA-21b. Prophylactic doses and dosing intervals will remain the same in the "Sub-Study Extension Phase" as in the last 2 months of Prophylactic Treatment-Phase II.

In case of unacceptable frequent and/or severe spontaneous breakthrough bleedings, the dose should be increased by approximately 5 IU/kg (depending on the entire content of vial(s) that needs to be reconstituted additionally). However, the maximum dose should not exceed 65 IU/kg. If, after a dose increase, patients still experience unacceptable bleeding episodes, the dosing interval should be shortened.

In addition, if the body weight of the patient during follow up visits fluctuates +/- 10% compared to the screening visit of the "Sub-Study Extension Phase", the investigator should verify if the dosing is still within the prescribed range and adapt accordingly, if necessary.

Duration of Treatment: The study duration for each patient in GENA-21b will be approximately 7–9 months.
The duration of the "Sub-Study Extension Phase" for each patient will be approximately between 2.5 and 3.5 years depending upon the completion date of the GENA-21b study.

Reference Therapy, Dose, and Mode of Administration: Not applicable; this is an open-label uncontrolled study.

Outcome Parameters

Primary Endpoint

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

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

Secondary Endpoints

1. Reduction of the annualised spontaneous bleeding rate* observed in the GENA-01 study (38.5 spontaneous bleeding episodes per patient per year) by 50% during individually tailored prophylaxis
2. Reduction of the annualised bleeding rate* observed in GENA-01 by 50% in patients with 2x/week prophylaxis or less
3. Median prophylactic dosing interval during individually tailored prophylaxis
4. Safety and tolerability of *Human-cl rhFVIII* by monitoring adverse events (AEs) throughout the study

Additional Endpoints

1. Descriptive efficacy of *Human-cl rhFVIII* in the treatment of breakthrough BEs
2. Descriptive efficacy of *Human-cl rhFVIII* in surgical prophylaxis
3. Correlation between VWF antigen concentration and half-life of *Human-cl rhFVIII*
4. Association between ABO blood type and half-life of *Human-cl rhFVIII*
5. *Human-cl rhFVIII* consumption data (FVIII IU/kg per month per patient) during individually tailored prophylaxis

Study Endpoints of the "Sub-Study Extension Phase" (Japan)

1. Safety of *Human-cl rhFVIII* by monitoring adverse events (AEs) and inhibitors against FVIII throughout the "Sub-Study Extension Phase"
2. The efficacy of *Human-cl rhFVIII* under prophylactic treatment will be assessed descriptively for the patients included in the "Sub-Study Extension Phase" by

* Total bleeding rate or bleeding rate refers to all types of bleeding (spontaneous, traumatic and other). A specific type of bleed is always described in text.

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

calculating the frequency of total and spontaneous break-through bleeds under individually tailored prophylaxis

3. Descriptive efficacy of *Human-cl rhFVIII* in the treatment of breakthrough BEs
4. Descriptive efficacy of *Human-cl rhFVIII* in surgical prophylaxis

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

Study Procedures

Screening Visit

The following assessments will be performed:

- Informed consent
- Eligibility criteria
- Demographic data: age, ethnic origin and blood type (ABO)
- Medical history
- Body weight
- Height
- Physical examination
- Vital signs (before blood sample collection)
- Routine safety lab
- CD4+
- Previous and concomitant medication (within one month before screening), including FVIII dosing in previous 6 months
- Hemophilia Joint Health Score (HJHS) (HJHS evaluation done in the 3 months prior to screening is acceptable)
- Target joint(s) (defined as three or more spontaneous bleeding episodes into a single joint within 6 consecutive months preceding screening visit)

Eligible patients agreeing to enter the study will receive a patient diary. The investigator will explain to the patient how to fill in the diary and emphasize the importance of carefully documenting all treatment details.

If possible, the Screening Visit may coincide with the Initial PK Visit. If it does not, any bleeding episodes occurring between the Screening Visit and the Initial PK Visit should be treated with the patient's previously used FVIII product. Similarly, prophylactic treatment between the Screening Visit and the Initial PK Visit should be done with the patient's previously used FVIII product. This has to be documented as concomitant medication in the diary and eCRF.

Initial PK Visit

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

Patients meeting the study entry criteria will receive *Human-cl rhFVIII* at a dose of 60 ± 5 IU/kg (labelled dose) after a washout period of at least 96 hours from their last FVIII injection. A washout period of at least 72 hours would be acceptable only if a patient is at a high risk of bleeding. Patients must not be experiencing any bleeding. The following assessments will be performed:

- Blood **samples** will be taken for the following purposes and at the following time points:
  - FVIII:C plasma concentration (one-stage and chromogenic assays): before injection (within 1 h before injection) and 0.5 h (± 5 min), 1 h (± 5 min), 3 h (± 15 min), 6 h (± 30 min), 9 h (± 1 h), 24 h (± 2 h), 30 h (± 2 h), 48 h (± 2 h), and 72 h (± 2 h), after the end of injection
  - VWFAg plasma concentration: before injection
  - FVIII inhibitor: before injection
- **Body weight** before injection
- **Vital signs** before injection as well as 1 and 72 hours after the end of injection
- **Information in the patient diary** (if applicable) will be reviewed by the Investigator.
- **IMP for home treatment** will be given to patients. They will be re-supplied whenever necessary during the study.

Prophylactic Treatment—Phase I

The 72-hour sampling time point of the Initial PK Visit marks the beginning of Prophylactic Treatment—Phase I, in which patients will be treated prophylactically every other day or 3x/week with a dose of 30–40 IU/kg BW for about 1–3 months until PK data have been analysed and discussed with the investigator. Throughout Prophylactic Treatment—Phase I, visits will take place according to the following schedule:

Day 14 Visit: will take place 14-21 days after the administration of the first dose of *Human-cl rhFVIII* on initial PK Visit day 1.

Day 30 Visit: will take place 30 days (± 3 days) after the administration of the first dose of *Human-cl rhFVIII* on initial PK Visit day 1.

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

- **Blood samples** for the determination of FVIII inhibitor will be obtained at these visits. Blood draw for inhibitor testing should be performed, preferably, when FVIII level has reached baseline.

End-of-Phase I Visit: At the end of Prophylactic Treatment—Phase I, the prophylactic dose and dosing interval will be determined for each patient based on the analysis of individual PK data as outlined in the dosing section. A blood sample will be taken for FVIII inhibitor testing during this visit, only if the End-of-Phase I Visit does not coincide with the Day 30 Visit.

Prophylactic Treatment—Phase II

Patients will be treated prophylactically for 6 months starting with the dose and dosing interval determined at the End-of-Phase I Visit. Extra prophylactic dosing prior to risky activities is permitted, but should be kept to a necessary minimum. Throughout Prophylactic Treatment—Phase II, visits will take place every 2 months.

2-Month Visit in Phase II: **The 2-Month Visit will take place 2 months (± 1 week) after the start of Prophylactic Treatment—Phase II.**

Note: To allow the patient's true trough levels to be determined, patients should be advised to present for blood sampling at the end of a regular treatment interval, i.e., *within 3 hours before injection of the next scheduled dose*.

The following assessments will be performed:

- **Blood samples** for the determination of FVIII:C trough levels (one-stage and chromogenic assays) and FVIII inhibitor will be obtained *within 3 hours before injection of the next scheduled FVIII dose*. Whenever an extra dose of FVIII has to be administered between scheduled prophylactic doses (e.g., for on-demand treatment of a bleeding episode), blood sampling for the determination of FVIII:C trough levels has to be delayed until the end of the next regular treatment interval.
- **Information in the patient diary** will be reviewed by the Investigator. For this purpose, the patient diaries will be collected and the data from completed diary pages transcribed to the eCRF.

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

4-Month Visit in Phase II: **The 4-Month Visit will take place 4 months (± 1 week) after the start of Prophylactic Treatment—Phase II and the same assessments will be done as at the 2-Month Visit in Phase II.**

The dose per injection may be reduced for the remainder of the study provided that FVIII:C trough levels (one-stage assay) obtained at the 2-Month Visit were ≥ 0.01 IU/mL and the patient has not experienced any spontaneous bleed up to the 4-Month Visit.

Monthly Compliance Checks

During Prophylactic Treatment—Phases I and II, monthly compliance checks (± 1 week) will be performed by telephone or during personal visits by the patient. The 1 month compliance check in Phase-I will be combined with the Day 30 Visit. During these checks, the investigator will determine whether the patient has adhered to the prescribed dose and dosing interval and whether the dose and dosing interval are adequate.

Study Completion Visit

The Study Completion Visit will take place 6 months (± 1 week) after the start of Prophylactic Treatment—Phase II

The following assessments will be performed:

- **Blood samples** will be taken:
  - FVIII:C plasma concentration (one-stage and chromogenic assays) for the determination of trough levels. Blood samples will again be obtained *within 3 hours before injection of the next scheduled FVIII dose*. Whenever an extra dose of FVIII has to be administered between scheduled prophylactic doses (e.g., for on-demand treatment of a bleeding episode), blood sampling for the determination of FVIII:C trough levels has to be delayed until the end of the next regular treatment interval. The next scheduled FVIII dose will no longer be considered study treatment.
  - FVIII inhibitor
- **Physical examination**

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

- **Information in the patient diary** will be reviewed by the Investigator. For this purpose, the patient diaries will be collected and the data from completed diary pages transcribed to the eCRF.
- All used and unused IMP vials will be returned by the patient.

Unscheduled visits

In case of positive inhibitor results, inhibitor retesting using a second, separately drawn sample should be performed, preferably within 15 days of becoming aware of the positive result. Other reasons for unscheduled visits may be the occurrence of serious AEs or hospitalizations due to severe bleeding episodes or surgical interventions.

Study Visits in the "Sub-Study Extension Phase" (Japan)

Screening Visit

Patients will be informed about the "Sub-Study Extension Phase" details and will be required to give a separate written informed consent before any investigations and any assessments can be performed. The screening visit should be performed in conjunction with the study completion visit of the GENA-21b study. The majority of data required will be available from the preceding GENA-21b completion visit, so that only the following information needs to be documented/assessed in addition:

- Check of inclusion- and exclusion criteria
- Body weight

The Investigator will hand out a patient diary and instruct the patient how to document details of treatment with *Human-cl rhFVIII*, bleeds, AEs and concomitant medication.

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

These visits will include assessment of FVIII inhibitor, FVIII:C trough levels, and body weight.

At such visits, each patient's body weight will be checked, and blood samples will be obtained for FVIII inhibitor screen and FVIII:C plasma concentration (one-stage and chromogenic assays) for the determination of trough levels. Blood samples will be obtained *within 3 hours before injection of the next scheduled FVIII dose*. The patient

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

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.

Completion Visit

For each patient, the "Sub-Study Extension Phase" is planned to be completed in the 4th quarter of 2020.
At this visit, patient's body weight will be checked, and blood samples will be obtained for FVIII inhibitor screen and FVIII:C plasma concentration (one-stage and chromogenic assays) for the determination of trough levels. 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.
In addition, all used and unused IMP vials will be returned by the patient.

Unscheduled visits

In case of positive inhibitor results, inhibitor retesting using a second, separately drawn sample should be performed, preferably within 15 days of becoming aware of the positive result. Other reasons for unscheduled visits may be the occurrence of serious AEs or hospitalizations due to severe bleeding episodes or surgical interventions.

Assessments and methods

Efficacy assessments

Bleeding episode (BE) data to be documented

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

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

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

- IMP dose(s) and batch number(s)
- Assessment of the efficacy of treatment at the end of the BE

All of these parameters will be documented by the patient (together with the investigator in case of on-site treatments) in the patient diary. Patients who experience a major or life-threatening BE should be treated at the study site.

At the end of a BE, treatment efficacy will be assessed by the patient (together with the investigator in case of on-site treatment) using the following predefined criteria:

- **Excellent:** Abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single injection
- **Good:** Definite pain relief and/or improvement in signs of bleeding within approximately 8–12 hours after an injection, requiring up to 2 injections for complete resolution
- **Moderate:** Probable or slight beneficial effect within approximately 12 hours after the first injection, requiring more than 2 injections for complete resolution
- **None:** No improvement within 12 hours, or worsening of symptoms, requiring more than 2 injections for complete resolution

The proportion of BEs **successfully treated** with IMP will be evaluated for all BEs taken together and by BE severity. All efficacy ratings assessed as either 'excellent' or 'good' will be considered 'successfully treated.'

Surgical prophylaxis

For any surgical procedure performed during the study, a predefined set of parameters will be recorded. Efficacy will be assessed at the end of surgery by the surgeon and at the end of the postoperative period by the haematologist. In addition, there will be an overall assessment of efficacy jointly made by the surgeon and the haematologist at the end of the postoperative period.

Efficacy of prophylactic treatment in the "Sub-Study Extension Phase" (Japan)

The efficacy of *Human-cl rhFVIII* in the prophylactic treatment will be assessed based on the frequency of total and spontaneous break-through bleeds under prophylactic treatment. The dates and times of study drug infusions, details of dose(s) and product batch numbers

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

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.

Safety assessments

Any of the following drug safety information shall be collected:

- Adverse events (AEs) and serious adverse events (SAEs) temporally associated with the administration of IMP
- Other relevant safety information, including post-study safety reports, instances of drug overdose, drug-drug interactions, abuse, misuse, medication error, or lack of efficacy

The severity of AEs will be graded as mild, moderate, or severe. The relationship of AEs to the administered IMP will be assessed by the responsible investigator and classified as probable, possible, unlikely, not related, or unclassified.

Laboratory assessments

The **routine safety laboratory tests** (as well as any FVIII:C measurements in case of surgery that may become necessary) will be done by the local laboratory. **FVIII:C** (one-stage and chromogenic assays), **FVIII inhibitor**, and **VWFAg** will be assessed by a central laboratory.

Statistical Analysis

Efficacy of individually PK tailored prophylactic regimen will be evaluated statistically based on comparison to 50% of the annualised total bleeding rate and the annualised spontaneous bleeding rate under on-demand treatment (data from study GENA-01). A confirmative one-sided one-sample Poisson-test will test whether the annualised total bleeding rate in patients with individual prophylaxis is at least 50% below the mean annualised total bleeding rate in the GENA-01 trial (i.e., if it is < 29).

As a secondary analysis of bleeding rates, the individual annualised bleeding rate will be analysed with a Poisson regression model and a Negative Binomial regression model. In

Name of Sponsor/Company: Octapharma AG, 8853 Lachen, Switzerland	
Name of Investigational Medicinal Product: Human-cl rhFVIII	**Protocol Identification Code:** GENA-21b
Name of Active Ingredient: Coagulation FVIII	**Date of Final Protocol:** Version 10, 24-Jul-2019

addition, GENA-21b individualised annualised bleeding rate data will be compared with GENA-01 individualised annualised bleeding rate data in these models; the estimated rate ratio comparing the individualised annual bleeding rates of the two trials will be provided with its 95% CI. This will be done for spontaneous, traumatic, and all BEs.

The statistical analysis of other secondary, additional, and safety endpoints will be descriptive.

Statistical Analysis for the "Sub-Study Extension Phase" (Japan)

No inferential analysis involving formal testing will be planned in this "Sub-Study Extension Phase". The patients are offered to continue treatment after the completion of the GENA-21b evaluation study in accordance with the study protocol; no formal sample size estimation is performed. The statistical analyses of the endpoints will be descriptive.

Schematic representation of the study by study phase and visit

Study phase	
Screening **Duration**: 28 days	**Screening Visit**
Initial PK Evaluation Phase **Duration**: 72 hours **Dose:** 60 ± 5 IU FVIII/kg	**Initial PK Visit** (may coincide with the Screening Visit)
Prophylactic Treatment—Phase I **Duration**: 1–3 months **Dose and dosing interval:** 30–40 IU/kg every other day or 3x/week	
Inhibitor test at Day 14	**Day 14 Visit**
Inhibitor test at Day 30	**Day 30 Visit /** Monthly compliance check at 1 month
	Monthly compliance check at 2 month
Inhibitor test at End of Phase I	**End-of-Phase-I Visit** (and beginning of Phase II)
Prophylactic Treatment—Phase II **Duration:** 6 months **Dose and dosing interval:** personalised	
	Monthly compliance check at 1 month
Trough levels (FVIII:C) and inhibitor test at 2 months	**2-Month Visit**
	Monthly compliance check at 3 months
Trough levels (FVIII:C) and inhibitor test at 4 months	**4-Month Visit***
	Monthly compliance check at 5 months
Trough levels (FVIII:C) and inhibitor test at 6 months	**Study Completion Visit/ Sub-Study Extension Phase Screening Visit**
Sub-Study Extension Phase for Japan **Duration:** 2.5-3.5 years **Dose and dosing interval:** personalised	
Trough levels (FVIII:C), inhibitor test and BW every 6 months	**Sub-Study Extension Phase 6-monthly Visit/Sub-Study Extension Phase Completion Visit**

* possibility for dose reduction based on FVIIII trough level at the 2M visit and bleeding status up to 4M visit in Phase II

PROTOCOL SIGNATURES

Signature of the Sponsor's Representative

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

Signature of the Author of the Protocol & Clinical Project Manager

This study is to be conducted in compliance with this protocol,
Good Clinical Practice, and applicable regulatory requirement s.

Signature of the Biostatist ician

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

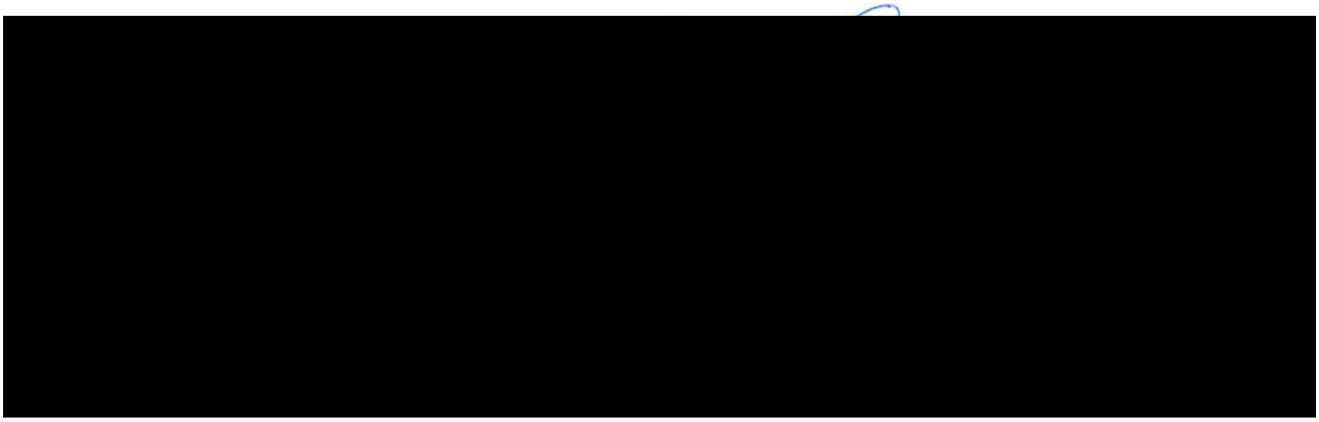


TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve (from baseline to infinity)
BE	bleeding episode
BU	Bethesda Unit
BW	body weight
CI	confidence interval
CL	clearance
C_{max}	maximum plasma concentration
CRF	Case Report Form
CRO	Contract Research Organisation
eCRF	electronic Case Report Form
ED	exposure day
EDC	electronic data capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
FVIII	factor VIII
FVIII:C	FVIII coagulant activity
GCP	Good Clinical Practice
HJHS	Hemophilia Joint Health Score
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IMP	investigational medical product
ITT	intention to treat
IU	International Unit
IVR	in-vivo recovery
MRT	mean residence time
PK	pharmacokinetic
PP	per protocol
PTPs	previously treated patients
rFVIII	recombinant FVIII
rhFVIII	recombinant human factor VIII
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
$t_{1/2}$	half-life
T_{max}	time to reach maximum plasma concentration
Vss	volume of distribution at steady state
VWFAg	von Willebrand factor antigen

1 INTRODUCTION

1.1 Background

Haemophilia A is an inherited sex-linked coagulation disorder in which affected males do not produce functional coagulation factor VIII (FVIII) in sufficient quantities to achieve satisfactory haemostasis, leading to bleeding diathesis. Most bleeding episodes (BEs) occur in the patient's joints and muscles. Without adequate treatment, repeated haemarthroses and haematoma lead to long-term sequelae with severe disability. Other bleeding sites, although less frequent but more severe, are the central nervous system, the urinary or gastrointestinal tract, the eyes, and the retroperitoneum. In addition, patients with haemophilia A are at high risk of developing major and life-threatening bleeding even after minor surgical interventions, such as tooth extractions.

The optimal treatment of haemophilia A is replacement of FVIII using FVIII product either obtained by fractionation of human plasma or manufactured by recombinant DNA technology. The transmission of viruses by plasma-derived coagulation factor concentrates in the 1970s and early 1980s sparked increased interest in producing FVIII products by recombinant DNA technology. The structure of the FVIII gene was elucidated in 1984, followed by the isolation of cDNA clones encoding the complete FVIII sequence and the in vitro expression of human FVIII in tissue culture. Since the early 1990s, recombinant FVIII products have been commercially available [1].

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

Human-cl rhFVIII is a fourth-generation recombinant human factor VIII (rhFVIII) product developed by Octapharma for the control and prevention of bleeding episodes and for surgical prophylaxis in patients with haemophilia A. It is a B-domain deleted rhFVIII produced in human embryonic kidney cells (HEK 293F) [4]. *Human-cl rhFVIII* has been shown to be highly pure, with host-cell protein and DNA traces comparable to, or lower than, currently marketed rFVIII products [5]. *Human-cl rhFVIII* has a high specific FVIII activity and characteristics similar to full-length rFVIII products. In functional tests, *Human-cl rhFVIII* exhibited physiological thrombin generation and a normal rate of inactivation by activated protein C. *Human-cl rhFVIII* displayed a higher binding capacity with von Willebrand factor (VWF) than comparator products, theoretically minimizing

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

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

Several clinical studies in a total of 201 previously treated adult and paediatric patients with severe haemophilia A have demonstrated the safety and efficacy of preventing and treating BEs with *Human-cl rhFVIII*. In particular, none of the patients developed an inhibitor against *Human-cl rhFVIII*.

1.2 Study Rationale

Prophylactic therapy is aimed at keeping the trough FVIII level above 1% between doses [7]. Traditionally, FVIIIproduct has been administered on alternate days or 3x/week for severe haemophilia A [8]. It was shown that trough FVIII concentrations and time per week with FVIII <0.01 IU per mL are mainly determined by the half-life and the dosing frequency [9]. To optimise prophylactic treatment, there is a call to individualise therapy in haemophilia, requiring knowledge of each patient's PK parameters in response to replacement factor, which is known to vary considerably between patients [10].

Individual differences between patients' PK parameters have also been observed in studies with *Human-cl rhFVIII*. For example, in adults, the mean ± SD half life of *Human-cl rhFVIII* as analysed using the one-stage assay for FVIII:C plasma concentrations was 17.1 ± 11.2 hours, the median half-life was 13.7 hours, and the 75% quantile was 17.5 hours. Efficient prophylaxis in adults, with a mean annualised bleeding rate of 2.3, was achieved with a mean ± SD dose of 32.8 ± 2.8 IU/kg, which in most cases (93.6%) was given every other day as stipulated by the study protocol.

The study GENA-21 was designed to investigate the efficacy and safety of personalised prophylaxis with *Human-cl rhFVIII* in previously treated adult patients (n=66) with severe haemophilia A in Europe with the aim to prolong the prophylactic injection intervals based

on analyses of individual patient's PK data. Results show that, in more than half of the patients, twice-weekly prophylactic injection was sufficient.

The current phase 3b study, GENA-21b, is also designed to investigate the efficacy and safety of personalised prophylaxis with *Human-cl rhFVIII* in previously treated adult patients with severe haemophilia A. The design of GENA-21b closely resembles that of GENA-21, and the study will collect further important data on the individualised prophylaxis approach worldwide.

"Sub-Study Extension Phase" to GENA-21b (Japan)

Once patients from treatment centres in Japan complete the study after 6 months in Prophylactic Treatment-Phase II and after performing the assessments of the completion visit, participants can decide to continue on the same treatment regimen and same product in a "Sub-Study Extension Phase" to GENA-21b.

The aim of the "Sub-Study Extension Phase" is to investigate the long-term safety and efficacy of *Human-cl rhFVIII* in patients included into the preceding study GENA-21b.

1.3 Dose Rationale

1.3.1 Initial PK Assessment

The **PK dose of 60 ± 5 IU/kg** in this study is the same as that used in the GENA-21 study and higher than in previous PK studies with *Human-cl rhFVIII*, in which the PK dose had been 50 IU/kg and the blood sampling period 48 hours. Considering the relatively long mean and median half-life of *Human-cl rhFVIII* as seen in GENA-01, it is expected that the higher dose in GENA-21b will result in measurable FVIII:C plasma concentrations after 72 hours in most, if not all, patients.

The ± 5 IU/kg range (rather than a fixed dose) was included to allow the entire contents of reconstituted vials to be injected rather than taking out an exact volume, which is difficult technically and might result in dosing errors.

1.3.2 Prophylactic Dose

The dosing recommendations for the **Prophylactic Treatment—Phase I (30–40 IU/kg every other day or 3x/week)** are the same as in GENA-21 as well as in previous studies in adults (GENA-08, treatment every other day) and children (GENA-03, treatment every other day or 3x/week).

In **Prophylactic Treatment—Phase II**, the PK-tailored dose and dosing interval will be determined individually for each patient. The goal is to determine the maximum regular prophylactic dosing interval that can be achieved with **a dose not exceeding 65 IU/kg** and capable of maintaining a trough level of ≥ 0.01 IU/mL.

By comparison, the goal of GENA-21 had been to determine the maximum regular prophylactic dosing interval that can be achieved with a dose of up to 80 IU/kg. The reason for changing the wording of the dosing recommendation from 'up to 80 IU/kg' in GENA-21 to a dose 'not exceeding 65 IU/kg' in GENA-21b is to motivate a further dose optimization with a view to further economizing on FVIII use.

1.3.3 Treatment of Bleeding Episodes and Surgical Prophylaxis

The dosing recommendations for the treatment of bleeding episodes and surgical prophylaxis in this study (see Section 6.4) are the same as in the preceding studies with adult patients (GENA-21, GENA-01, GENA-08).

1.3.4 Treatment with *Human-cl rhFVIII* during the "Sub-Study Extension Phase" (Japan)

Patients will continue to be treated prophylactically after the completion of 6 months in Treatment-Phase II in GENA-21b. Prophylactic doses and dosing intervals will remain the same in the "Sub-Study Extension Phase" as in the last 2 months of Prophylactic Treatment-Phase II.

In case of unacceptable frequent and/or severe spontaneous breakthrough bleedings, the dose should be increased by approximately 5 IU/kg (depending on the entire content of vial(s) that needs to be reconstituted additionally). However, the maximum dose should not exceed 65 IU/kg. If, after a dose increase, patients still experience unacceptable bleeding episodes, the dosing interval should be shortened.

In addition, if the body weight of the patient during follow up visits fluctuates +/- 10% compared to the screening visit, the investigator should verify if the dosing is still within the prescribed range and adapt accordingly, if necessary.

Dosing recommendations for the treatment of bleeding episodes and for surgical prophylaxis are the same as in the preceding study (see section 6.4).

1.4 Benefit-Risk Statement

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

The following adverse drug reactions (ADRs) have been observed with commercially available rFVIII preparations and may also occur with *Human-cl rhFVIII*:

- Hypersensitivity or allergic type of reactions. Observed symptoms may include hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. Rarely, such reactions may progress to severe anaphylaxis, including shock.
- Development of antibodies (inhibitors) against FVIII.

Considering all currently available nonclinical and clinical observations, including pharmacokinetic (PK) data, it may be assumed that participation in this study does not present any additional risk.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this clinical study is to compare the annualised total bleeding rate of individually tailored prophylaxis with the historical bleeding rate observed in patients having received on-demand treatment with *Human-cl rhFVIII* from study GENA-01.

2.2 Secondary Objectives

The secondary objectives of this clinical study are

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

2.3 Additional Objectives

Additional objectives of this clinical study are

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

2.4 Objectives of the "Sub-Study Extension Phase" to GENA-21b (Japan)

1. To investigate the long-term safety of *Human-cl rhFVIII* in patients with severe haemophilia A who participated in the GENA-21b study
2. To assess the long-term efficacy of *Human-cl rhFVIII* during prophylactic treatment (based on the frequency of total and spontaneous break-through bleeds)
3. To assess the efficacy of *Human-cl rhFVIII* during treatment of bleeding episodes (BEs)
4. To assess the efficacy of *Human-cl rhFVIII* in surgical prophylaxis

3 INVESTIGATIONAL PLAN

3.1 Primary Endpoint

The primary endpoint of this study is the reduction of the annualised total bleeding rate observed in the GENA-01 study (58.1 total bleeding episodes per patient per year) by 50% during individually tailored prophylaxis.

3.2 Secondary Endpoints

1. Reduction of the annualised spontaneous bleeding rate observed in the GENA-01 study (38.5 spontaneous bleeding episodes per patient per year) by 50% during individually tailored prophylaxis
2. Reduction of the annualised bleeding rate observed in GENA-01 by 50% in patients with 2x/week prophylaxis or less
3. Median prophylactic dosing interval during individually tailored prophylaxis
4. Safety and tolerability of *Human-cl rhFVIII* by monitoring adverse events (AEs) throughout the study

3.3 Additional Endpoints

1. Descriptive efficacy of *Human-cl rhFVIII* in the treatment of breakthrough BEs
2. Descriptive efficacy of *Human-cl rhFVIII* in surgical prophylaxis
3. Correlation between VWF antigen concentration and the half-life of *Human-cl rhFVIII*
4. Association between ABO blood type and half-life of *Human-cl rhFVIII*
5. *Human-cl rhFVIII* consumption data (FVIII IU/kg per month per patient) during individually tailored prophylaxis

3.4 Endpoints of the Sub-Study (Japan)

1. Safety of *Human-cl rhFVIII* by monitoring adverse events (AEs) and inhibitors against FVIII throughout the “Sub-Study Extension Phase”
2. The efficacy of *Human-cl rhFVIII* under prophylactic treatment will be assessed descriptively for the patients included in the “Sub-Study Extension Phase” by calculating the frequency of total and spontaneous break-through bleeds under individually tailored prophylaxis treatment

3. Descriptive efficacy of *Human-cl rhFVIII* in the treatment of breakthrough BEs
4. Descriptive efficacy of *Human-cl rhFVIII* in surgical prophylaxis

4 OVERALL STUDY DESIGN

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

Approximately 55 male subjects ≥ 18 years of age will be enrolled with the aim to have evaluable data on 50 subjects. Subjects will be recruited from about 30 haemophilia treatment centres worldwide.

The study consists of three (3) phases, i.e., the PK Evaluation Phase, the Prophylactic Treatment—Phase I, and the Prophylactic Treatment—Phase II. After Prophylactic Treatment-Phase II a "Sub-Study Extension Phase" to continue the treatment with *Human-cl rhFVIII* and to investigate long-term safety and efficacy will be offered to patients from study centres in Japan.

- The **PK Evaluation Phase** will last for 72 hours (i.e., 3 days).
- The purpose of **Prophylactic Treatment—Phase I**, which will last for 1–3 months, is to treat the patients prophylactically every other day or 3x/week with a dose of 30–40 IU/kg BW until individual PK data have been analysed and discussed with the investigator .
- In **Prophylactic Treatment—Phase II**, Prophylactic doses and dosing intervals will be recommended by the Sponsor for each patient based on the analysis of individual PK data obtained at the Initial PK Visit with the one-stage assay. The final decision on the prophylactic scheme will be taken by the investigator after consultation with the patient and Sponsor.

The study duration for each patient will be approximately 7–9 months, and the GENA-21b study duration will be about 3 years. The investigator will inform the monitor of any recruitment difficulty or delay in the anticipated completion date. The end of the GENA-21b study is defined as the last visit of the last patient participating in the study.

"Sub-Study Extension Phase" to GENA-21b (for Japan)

After completing the GENA-21b study which is defined as 6 months of prophylactic treatment in Treatment-Phase II and after performing the assessments of the completion visit, participants can decide to continue on the same treatment regimen with *Human-cl rhFVIII* in a "Sub-Study Extension Phase" to GENA-21b.

This "Sub-Study Extension Phase" will be offered to patients from study centres in Japan. Approximately 10 patients from Japan are expected to enrol into the GENA-21b study. Therefore approximately 10 patients may continue treatment in the "Sub-Study Extension Phase".

The "Sub-Study Extension Phase" will start individually for each patient with the completion visit of GENA-21b and the screening visit for the "Sub-Study Extension Phase", which should occur on the same day. The treatment is planned until the 4th quarter in 2020.

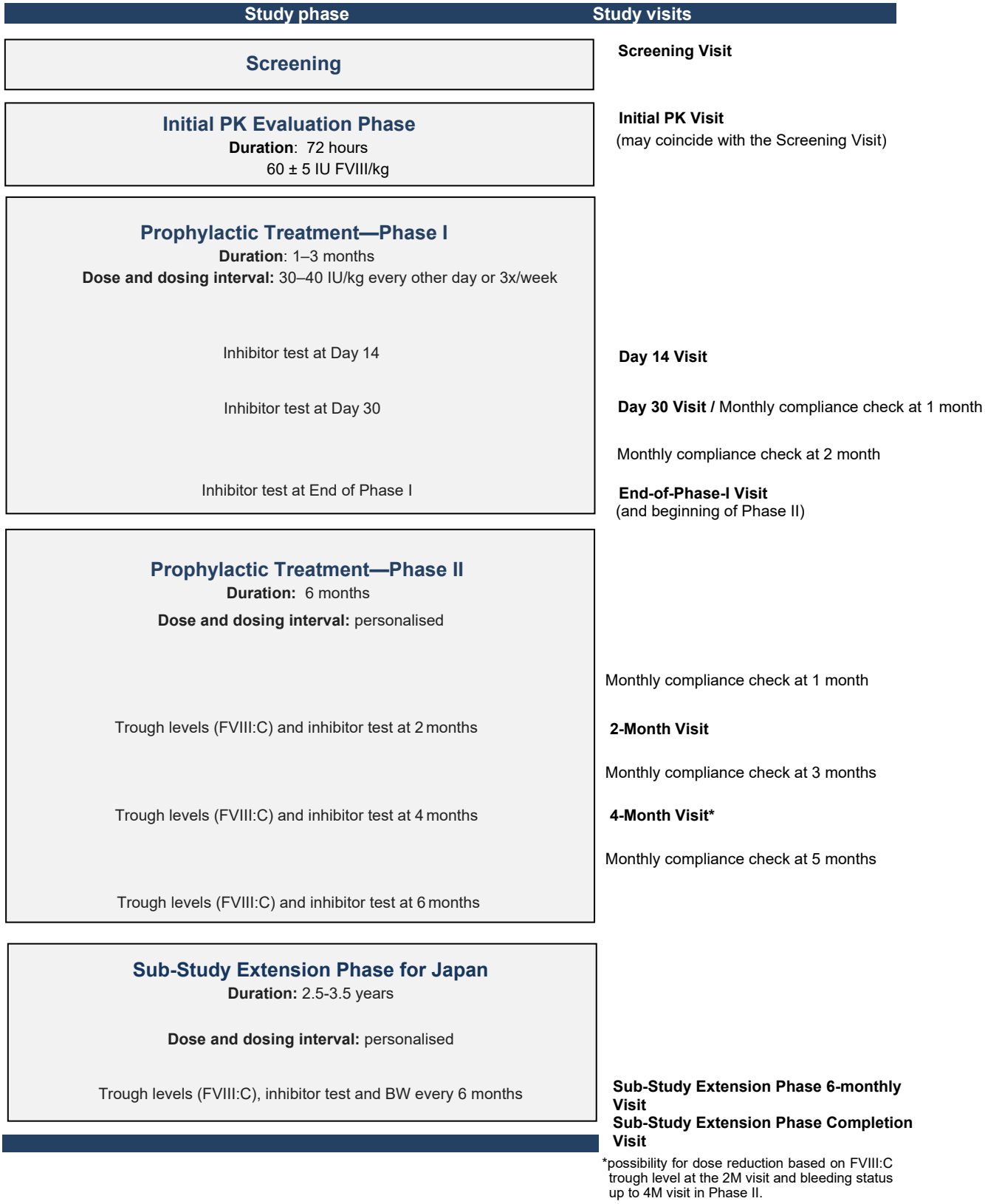
While in the "Sub-Study Extension Phase", patients will be monitored every 6 months for FVIII inhibitors and FVIII:C trough levels. Patients will be handed a diary to continue recording adverse events, concomitant medications, treatment of bleeding episodes, prophylactic treatments, and the use of *Human-cl rhFVIII* within surgeries, if needed.

Patients are eligible to participate in the "Sub-Study Extension Phase" if they completed the GENA-21b study with 6 months of prophylactic treatment in Treatment-Phase II and voluntarily gave fully informed written and signed consent before any Sub-Study related procedures are conducted.
The completion visit of the GENA-21b study and the screening visit for the "Sub-Study Extension Phase" should occur on the same day.
The patients should not have received any other FVIII product than *Human-cl rhFVIII* between completion visit of GENA-21b study and start of "Sub-Study Extension Phase" (except emergency cases).

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

A schematic representation of the study by study phase and visit is given in Figure 1.

Figure 1 Schematic representation of the study by study phase and visit



4.1 Discussion of Study Design

The rationale of this study is to further fine-tune and individualise prophylactic treatment of patients with severe haemophilia A (see Section 1.2).

The treatment needs of patient with haemophilia A are highly variable due to the heterogeneity of their bleeding phenotype, joint status, and type and intensity of physical activity [11]. Ideally, a multi-dimensional approach should be adopted in tailoring and monitoring prophylactic regimens, taking into account bleeding symptoms, laboratory data (factor trough levels, PK), joint status, quality of life, and treatment costs [11].

Because trough FVIII levels are likely to be important predictors of the efficacy of prophylaxis, the focus in this study is on PK data. The time spent below a certain factor level and trough FVIII levels depend on the dose and frequency of FVIII injections and on the individual PK parameters in response to injected FVIII. For the calculation of individual prophylactic dosing and dosing interval, we assume that effective prophylaxis against bleeding is maintained if plasma FVIII coagulant activity (FVIII:C) is kept above 1%, although it is known that some patients do not bleed despite a trough level < 1%, whereas other patients bleed with trough levels > 3% [12].

In addition, the rationale for the "Sub-Study Extension Phase" is to investigate the long-term safety and efficacy of *Human-cl rhFVIII* in patients included into the preceding study GENA-21b.

4.1.1 Assays used to determine the response to FVIII treatment

In this study, two assays for the determination of FVIII plasma levels will be used, i.e., the **one-stage assay** and the **chromogenic assay**.

For the PK analyses in the present study, we will use the results of FVIII:C one-stage measurements, because this is the more widely used assay in clinical practice. Discrepancies in factor half-life have been reported between one-stage and two-stage/chromogenic methods in clinical use [13]. In our previous PK study in adults (GENA-01), however, the discrepancies in the half-life between the two assays were not pronounced.

4.1.2 Effectiveness of prophylactic treatment with *Human-cl rhFVIII*: 50% reduction in the number of bleeding episodes per patient per year compared with on-demand treatment in GENA-01

In **GENA-01**, the efficacy and safety of **on-demand treatment** with *Human-cl rhFVIII* for at least 6 months and at least 50 exposure days (EDs) were evaluated in 22 adolescent and

adult PTPs with severe haemophilia A. The mean number of bleeding episodes per patient per year in GENA-01 was 58.1.

GENA-08 and **GENA-09** determined the efficacy of **prophylactic treatment** with *Human-cl rhFVIII* every other day in 32 and 22 adult PTPs with severe haemophilia A for at least 6 months and at least 50 EDs. While GENA-08 was performed as a multicentre study in several, mainly Western European, countries, GENA-09 was a single-centre study in Russia in a patient population that had been inadequately treated since childhood. As agreed with the US Food and Drug Administration (FDA), prophylactic treatment with *Human-cl rhFVIII* in GENA-08 was to be considered effective if a 50% reduction in the total number of bleeding episodes per patient per year was observed compared to GENA-01 where on-demand treatment was used. The EMA Guideline gives no guidance as to how exactly assess the efficacy of prophylaxis. In the GENA-21 study, the same approach to demonstrate the effectiveness of prophylactic treatment with *Human-cl rhFVIII* as agreed with the FDA was chosen.

4.1.3 Rationale for Treatment Duration

EMA guideline EMA/CHMP/BPWP/144533/2009 states that for 'the assessment of clinical efficacy of FVIII in long-term prophylaxis, patients should be treated for 6 months and assessed for bleeding episodes, bleeding intervals and number of treatments.' As for previous studies with *Human-cl rhFVIII* (i.e., GENA-08 in adolescent/adult patients and GENA-03 in paediatric patients), the duration of the Prophylactic Treatment—Phase II in GENA-21b is 6 months.

The Sub-Study is an extension to the GENA-21b study to allow patients in Japan to stay on *Human-cl rhFVIII* after completing the prophylactic treatment of 6 months in Prophylactic Treatment-Phase II and with the goal to investigate long-term safety and efficacy of *Human-cl rhFVIII.*

Provided the inclusion- and exclusion criteria are met, all subjects wishing to continue the prophylaxis treatment with *Human-cl rhFVIII* will be included into the "Sub-Study Extension Phase". The individual study participation period varies depending upon completion of Treatment-Phase II.

The first patient in Japan completed Treatment-Phase-II of GENA-21b in June 2017 and the last completed Treatment-Phase-II in September 2018. The clinical study end of the "Sub-Study Extension Phase" is planned to be in the 4th Quarter of 2020. Thus, individual study duration in the "Sub-Study Extension Phase" may vary from approximately 2.5 to 3.5 years.

The overall study duration from start of the GENA-21b in the 2nd Quarter of 2015 until "Sub-Study Extension Phase" completion visit in the 4th Quarter of 2020 is approximately 5.75 years.

5 STUDY POPULATION

The goal of the GENA-21b study is to collect data on **50 patients** who complete the 6-month Prophylactic Treatment—Phase II of this study. Approximately 55 patients will be enrolled to compensate for potential drop-outs.

The goal of the "Sub-Study Extension Phase" is to collect long-term safety and efficacy data from approximately 10 patients in Japan. Potential drop outs will not be replaced because only patients who completed the GENA-21b study will be eligible to participate in the "Sub-Study Extension Phase".

5.1 Inclusion Criteria

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

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

Inclusion criteria for "Sub-Study Extension Phase" (Japan):

(a) Patients who completed the GENA-21b study with 6 months of prophylactic treatment in Treatment Phase II
(b) Voluntarily given, fully informed written and signed consent obtained before any "Sub-Study (Extension Phase)"-related procedures are conducted

5.2 Exclusion Criteria

Patients who meet any of the following criteria are *not* eligible for the study:

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

Exclusion criteria for "Sub-Study Extension Phase" (Japan):

(a) Other FVIII product than *Human-cl rhFVIII* was received between completion visit of GENA-21b study and start of "Sub-Study Extension Phase" (except emergency cases).

5.3 Concomitant Therapy

5.3.1 Permitted Concomitant Therapy

Concomitant therapies not interfering with the objectives of the study are permitted. Details of any concomitant medication must be recorded in the electronic Case Report Form (eCRF).

Any bleeding episodes occurring between the Screening Visit and the Initial PK Visit should be treated with the patient's previously used FVIII product. Similarly, prophylactic treatment between the Screening Visit and the Initial PK Visit should be done with the patient's previously used FVIII product.

5.3.2 Prohibited Concomitant Therapy

No other FVIII product should be given (except for emergency situations).

Patients who switch to another FVIII product during their study participation will **not** be considered treatment failures in the efficacy analyses if:

- the use of another FVIII product was due to an emergency (example: accident requiring treatment with FVIII without the patient (or intensive care unit personnel) having access to the IMP)
- the IMP was not available to the patient in time (example: patient experiences severe bleed but has not enough IMP available at home)

The switch to another FVIII product is allowed in case the IMP does not achieve the therapeutic results as expected e.g., when patients experience continued bleeding despite the correct administration of coagulation factors (lack of efficacy). In this case the patients will be considered treatment failures and their study participation will be discontinued. Lack of efficacy is considered an adverse event or serious adverse event, as applicable (see section 8.3.5).

5.4 Premature Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason without the need to justify their decision. The investigator also has the right to withdraw patients in case of AEs or protocol violations or for other reasons. Because an excessive rate of withdrawals may render the study noninterpretable, unnecessary withdrawals of patients should be avoided.

In case of any discontinuation after study entry, the investigator will collect all the required details and document the reason(s) for discontinuation in the eCRF. If the reason for withdrawal of a patient is an AE, the main specific event or laboratory test will be recorded in the eCRF, and the investigator will make every possible effort to clearly document the outcome.

5.4.1 Patient Replacement Policy

Patients withdrawn from the study will not be replaced.

5.5 Assignment of Patients to Treatment Groups

Not applicable; this is an uncontrolled study.

5.6 Relevant Protocol Deviations

In case of a major protocol deviation or violation, the investigator and Sponsor will decide on the further participation of the patient in this study after having considered all relevant aspects.

5.7 Subsequent Therapy

At the end of Treatment-Phase II of the GENA-21b study, patients will continue substitution therapy using a commercially available FVIII product or they can continue treatment with *Human-cl rhFVIII* in the “Sub-Study Extension Phase” after signing informed consent.

At the end of the “Sub-Study Extension Phase” patients will continue substitution therapy using a commercially available FVIII product.

6 INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Characterisation of Investigational Medicinal Product

The IMP *Human-cl rhFVIII* is a human cell line derived B-domain deleted rFVIII product for intravenous use. Each vial contains either 250, 500, 1000, ;2000, 2500, 3000, or 4000 international units (IU) of freeze-dried *Human-cl rhFVIII* product to be reconstituted in 2.5 mL of water for injections (WFI) each. In this study, several batches of product will be used.

6.2 Packaging and Labelling

The IMP, i.e., the vial with *Human-cl rhFVIII* freeze-dried product, will be provided together with the diluent (2.5 mL of WFI in pre-filled syringe) and the necessary equipment to enable IMP administration. The final labelling will comply with the national requirements of each country where the study is conducted.

6.3 Conditions for Storage and Use

The product has to be stored at 2°C to 8°C and protected from light. Use the reconstituted solution immediately or within 3 hours after reconstitution. Keep the reconstituted solution at room temperature. Do not refrigerate after reconstitution.

Do no freeze. Any remaining solution should be discarded.

Do not use after the expiration date.

The investigator or any authorised site personnel will ensure that the IMP is stored in appropriate conditions with restricted access and in compliance with national regulations. The investigator will advise the patient with regard to the necessary conditions for the storage of the IMP during home treatment.

6.4 Dose and Dosing Interval

The doses and dosing intervals used in this study vary with the study phase. For a schematic representation of the study by visit and study phase, see Figure 1. For a detailed description of the study visits, see Section 7.2.

6.4.1 Initial PK Visit

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

6.4.2 Prophylactic Treatment—Phase I

The 72-hour sampling time point of the Initial PK Visit marks the beginning of Prophylactic Treatment—Phase I, in which patients will be treated prophylactically every other day or 3x/week with a dose of 30–40 IU/kg BW for about 1–3 months until PK data have been analysed and discussed with the investigator.

Dose escalations are allowed in case of an inadequate frequency and severity of breakthrough bleeding episodes in accordance with the institution's standard clinical care.

If patients receive a dose of 40 IU/kg BW and experience unacceptable frequent and/or severe spontaneous breakthrough bleedings only one further dose escalation is allowed for the maximum dose not to exceed 45 IU/kg BW.

6.4.3 Prophylactic Treatment—Phase II

In this phase, patients will be treated prophylactically for 6 months.

The prophylactic dose and injection interval will be recommended by the Sponsor for each patient based on the analysis of individual PK data obtained with the one-stage assay at the Initial PK Visit.

Based on an appropriate PK model, various dosing intervals (usually 12-hour intervals) and corresponding doses (in IU/kg) will be calculated, which theoretically lead to FVIII:C plasma concentrations of at least 0.01 IU/mL at the end of the respective injection interval.

The goal is to use the maximum regular prophylactic dosing interval that can be achieved with a maximum dose of not more than 65 IU/kg and that maintains a trough level of ≥ 0.01 IU/mL.

This recommendation may change in certain situations. For example,

- If the maximum calculated dosing interval is ≤ 2.5 days, the recommendation may be to continue with the dose and dosing interval as used in Prophylactic Treatment—Phase I, provided that this treatment scheme was considered effective by both the treating physician and the patient.
- If the maximum calculated dosing interval is > 3.5 days and the dose > 65 IU/kg, the recommendation may be to reduce the dosing interval by 0.5 days and use the corresponding lower dose.

- If the maximum calculated dosing interval is ≥ 4.5 days, the recommendation may be to reduce the dosing interval by 0.5 days and use the corresponding dose.

In general, the recommendation will take into account both the interpretation of the PK data as well as practical and economic aspects (i.e., consumption of FVIII).

The final decision on the prophylactic scheme will be taken by the investigator after consultation with the patient and Sponsor.

At the 4-Month Visit in Prophylactic Treatment—Phase II, the dose per injection for the remainder of the study may be reduced provided that FVIII:C trough levels (one-stage assay) obtained at the 2-Month Visit were ≥ 0.01 IU/mL and the patient has not experienced any spontaneous bleed up to the 4-Month Visit.

Extra prophylactic dosing prior to risky activities is permitted and has to be documented.

In case of unacceptable frequent and/or severe spontaneous breakthrough bleedings, the dose should be increased by approximately 5 IU/kg (depending on the entire content of vial(s) that needs to be reconstituted additionally). However, the maximum dose should not exceed 65 IU/kg. If, after a dose increase, patients still experience unacceptable bleeding episodes, the dosing interval should be shortened.

6.4.3.1 Dosing in “Sub-Study Extension Phase” to GENA-21b

In this “Sub-Study Extension Phase” patients will continue their prophylactic treatment as prescribed during the last 2 months in Treatment-Phase II.

Extra prophylactic dosing prior to risky activities is permitted and has to be documented.

In case of unacceptable frequent and/or severe spontaneous breakthrough bleedings, the dose should be increased by approximately 5 IU/kg (depending on the entire content of vial(s) that needs to be reconstituted additionally). However, the maximum dose should not exceed 65 IU/kg. If, after a dose increase, patients still experience unacceptable bleeding episodes, the dosing interval should be shortened.

In addition, if the body weight of the patient during follow up visits fluctuates +/- 10% compared to the screening visit, the investigator should verify if the dosing is still within the prescribed range and adapt accordingly, if necessary.

6.4.4 Treatment of Bleeding Episodes

The dosage and duration of treatment of spontaneous or traumatic breakthrough bleeding episodes (BEs) will depend on the location and extent of bleeding and on the clinical situation of the patient.

The following general dosage recommendations are given:

- **Minor haemorrhage:** 20–30 IU FVIII/kg every 12–24 hours until bleeding episode is resolved.
- **Moderate to major haemorrhage:** 30–40 IU FVIII/kg. Repeat one dose every 12–24 hours until bleeding episode is resolved.
- **Major to life-threatening haemorrhage:** initial dose of 50–60 IU FVIII/kg. Repeat dose of 20–25 IU FVIII/kg every 8–12 hours until bleeding episode is resolved.

6.4.5 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.

The following general dosage recommendations are given:

- **Minor surgeries, including tooth extractions:** 25–30 IU FVIII/kg BW within 3 hours prior to surgery to achieve an intended target peak level of about 50% to 60%. Repeat one dose every 12–24 hours if needed. Trough levels should be maintained at approximately 30% (samples taken prior to the next injection of IMP).
- **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 days until healing is complete. Trough levels should be maintained at approximately 50% (samples taken prior to the next injection of the IMP).

6.5 Preparation and Method of Administration

Each vial of *Human-cl rhFVIII* will be reconstituted in 2.5 mL WFI. Detailed handling instructions will be provided.

Before injection, the solution must reach room temperature without applying any specific warming-up measures. The solution should be administered within 3 hours after reconstitution on only one occasion. The solution is normally clear or slightly opalescent and colourless. Solutions which are cloudy or have deposits must not be used.

Human-cl rhFVIII should be injected intravenously by bolus injection at a maximum rate of 4 mL/min using an aseptic technique.

6.6 Blinding, Emergency Envelopes and Breaking the Study Blind

Not applicable; this is an open-label study.

6.7 Treatment Compliance

6.7.1 Drug Dispensing and Accountability

A drug dispensing log and the inventory will be kept current by the investigator, detailing the dates and quantities of IMP dispensed to each patient. The inventory will be available to the monitor to verify drug accountability during the study. Patients will be advised to return any used vials and expired IMP at each study visit and to return any used vials and unused IMP at the Study Completion Visit. Any unused IMP, either not dispensed or returned by the patient, will be accounted for.

Unused IMP will be returned to the Sponsor or can be destroyed at the study site after written approval from the Sponsor has been obtained. When required by local policies, unused IMP may be destroyed at the study site after drug accountability has been verified and fully reconciled and written approval from the Sponsor has been obtained.

6.7.2 Assessment of Treatment Compliance

Treatment compliance will be verified on the basis of patient diaries and monthly compliance checks in Treatment-Phases I and II. During the "Sub-Study Extension Phase" compliance will be checked during 6-monthly follow up visits.

Patient diaries

Patients will usually treat themselves at home, and they will therefore be provided with a sufficient amount of IMP and a patient diary.

The patient diary will be handed to the patient during the Screening Visit after inclusion into the study. The investigator will explain to the patient how to fill in the diary and emphasize the importance of carefully documenting all treatment details.

The following data will be recorded in the patient diary:

- The recording of self-injections includes the date and time of administration as well as the dose, batch number, and reason for injection (i.e., prophylaxis, BE treatment). For BE data to be documented, see Section 8.2.1.
- Concomitant medications
- Adverse events (AEs)

At each follow-up visit at the study site, the patient will bring along all diaries for review and validation by site personnel and return any used vials and unused expired IMP (see Section 6.7.1).

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

Monthly compliance checks

During Prophylactic Treatment—Phases I and II, monthly compliance checks (± 1 week) will be performed by telephone or during personal visits by the patient. For more information on the monthly compliance checks, refer to Section 7.2.5.

7 STUDY CONDUCT

7.1 Flow Chart of Assessments

The flow chart of assessments performed throughout the entire study is given in Table 1.

Table 1 Flow Chart of Assessments Performed Throughout the Study

Asessments	Screening Visit[1]	Initial PK Visit[1]	Day 14 Visit	Day 30 Visit[14]	End-of- Phase-I Visit (and beginning of Phase II)	2-Month Visit[2]	4-Month Visit[2]	Study Completion Visit[2/16]
		after washout period of ≥ 96 h after last FVIII administration[15] (see Table 2)	14-21 days after initial PK Visit day	30 days (± 3 days) after initial PK Visit day	1–3 months after Initial PK Visit	2 months (± 1 week) after beginning of Prophylactic Treatment—Phase II	4 months (± 1 week) after beginning of Prophylactic Treatment—Phase II	6 months (± 1 week) after beginning of Prophylactic Treatment—Phase II
Informed consent	x							
Eligibility criteria	x							
Demographics	x							
Medical history	x							
Body weight	x	x						
Height	x							
Physical examination	x							x
Vital signs[3]	x	x[4]						
Routine safety lab[5]	x							
CD4+[6]	x							
Previous medication	x							
Hemophilia Joint Health Score (HJHS)[12]	x							
FVIII:C plasma concentration[7]		x				x[8]	x[8]	x[8]
von Willebrand factor antigen (VWFAg)		x						
FVIII inhibitor [13]		x	x	x	x	x	x	x
Review of patient diary		x[9]			x	x	x	x
Prophylactic dose and dosing interval					x[10]		x[11]	
Adverse event (AE) monitoring	Throughout the study							
Concomitant medication	Throughout the study							
Efficacy of *Human-cl rhFVIII* in the treatment of bleeding events (BEs)	Throughout the study							
Efficacy of *Human-cl rhFVIII* in surgical prophy-laxis	Throughout the study							

[1] If possible, the Screening Visit may coincide with the Initial PK Visit.

[2] Throughout Prophylactic Treatment—Phase II, visits will take place every 2 months.

[3] Systolic and diastolic blood pressure, body temperature, pulse

[4] Before injection as well as 1 and 72 hours after the end of injection.

[5] Haematology (local lab): red blood cell count, white blood cell count, haemoglobin, haematocrit, platelet count. Clinical chemistry (local lab): total bilirubin, ALT, AST, urea, serum creatinine, lactate dehydrogenase.

[6] Local lab.

[7] Central lab, using both one-stage and chromogenic assays.

[8] For the determination of FVIII:C trough plasma concentrations. Blood samples should be taken *within 3 hours before injection of the next scheduled FVIII dose*. Whenever an extra dose of FVIII has to be administered between scheduled prophylactic doses (e.g., for on-demand treatment of a bleeding episode), blood sampling for the determination of FVIII:C trough levels has to be delayed until the end of the next regular treatment interval.

[9] If the Screening Visit and the Initial PK Visit do not coincide.

[10] At the end of Prophylactic Treatment—Phase I, the prophylactic dose and dosing interval will be decided for each patient based on the analysis of individual PK data.

[11] The dose per injection may be reduced for the remainder of the study based FVIII:C trough levels (one-stage assay) obtained at the 2-Month Visit and provided the patient has not experienced any spontaneous bleed up to the 4-Month Visit.

[12] Version: HJHS 2.1 [14]

[13] Inhibitor testing should be performed, preferably, when FVIII level has reached baseline.

[14] Day 30 may coincide with End of Phase I Visit.

[15] A washout period of at least 72 hours would be acceptable only if a patient is at a high risk of bleeding.

[16] If patients continue treatment in the "Sub-Study Extension Phase" after the completion visit, the completion visit data will also be used as the screening data for the "Sub-Study Extension Phase". If possible, both visits should occur on the same day.

Table 2 Flowchart of Assessments in the "Sub-Study Extension Phase"

	Completion visit GENA-21b/Screening Visit "Sub-Study Extension Phase"	6-monthly (+/- 2 weeks) follow up visits	Completion visit of "Sub-Study Extension Phase"
Written informed consent	✓		
Inclusion/exclusion criteria check	✓		
Body weight	✓	✓	✓
Physical Exam	✓		✓
Diary & IMP instructions	✓		
FVIII inhibitor/ FVIII:C (trough)	✓	✓	✓
Review of diary	<throughout whole period>		
AE monitoring & changes in concomitant medication	<throughout whole period>		
Efficacy of Human-cl rhFVIII in the treatment of bleeding events (BEs)	throughout whole period		
Efficacy of Human-cl rhFVIII in surgical prophylaxis	throughout whole period		

7.2 Observations by Visit

For a schematic representation of the study design by visit and study phase, see Figure 1.

7.2.1 Screening Visit

The following assessments will be performed:

- **Informed consent**
- **Eligibility criteria**
- **Demographic data**: age, ethnic origin and blood type (ABO)
- **Medical history** (including FVIII inhibitor history, HIV status, and bleeding frequency in the previous 6 months)
- **Body weight**
- **Height**
- **Physical examination**
- **Vital signs** (systolic and diastolic blood pressure, body temperature, pulse) before blood sample collection
- **Routine safety lab** (haematology [red blood cell count, white blood cell count, haemoglobin, haematocrit, platelet count] and clinical chemistry [total bilirubin, ALT, AST, urea, serum creatinine, lactate dehydrogenase])
- **CD4+**
- **Previous and concomitant medication** (within one month before screening), including FVIII dosing in previous 6 months
- **Hemophilia Joint Health Score (HJHS)** [14]. HJHS evaluation done in the 3 months prior to screening is acceptable. HJHS 2.1 summary score sheet should be used [14]
- **Target joint(s)** (defined as three or more spontaneous bleeding episodes into a single joint within 6 consecutive months preceding screening visit)

Eligible patients agreeing to enter the study will receive a patient diary (see Section 6.7.2).

The Screening Visit may coincide with the Initial PK Visit. If it does not, any bleeding episodes occurring between the Screening Visit and the Initial PK Visit should be treated with the patient's previously used FVIII product. Similarly, prophylactic treatment between the Screening Visit and the Initial PK Visit should be done with the patient's previously used FVIII product. This has to be documented as concomitant medication in the diary and eCRF.

7.2.2 Initial PK Visit

Patients meeting the study entry criteria will receive *Human-cl rhFVIII* at a dose of 60 ± 5 IU/kg (labelled dose) after a washout period of at least 96 hours from their last FVIII injection. A washout period of at least 72 hours would be acceptable only if a patient is at a high risk of bleeding. Patients must not be experiencing any bleeding.

The following assessments will be performed:

- **Blood samples** will be taken for the following purposes and at the following time points (see also Table 3):
  - FVIII:C plasma concentration (one-stage and chromogenic assays):* before injection (within 1 h before injection) and 0.5 h (± 5 min), 1 h (± 5 min), 3 h (± 15 min), 6 h (± 30 min), 9 h (± 1 h), 24 h (± 2 h), 30 h (± 2 h), 48 h (± 2 h), and 72 h (± 2 h), after the end of injection
  - VWFAg plasma concentration: before injection
  - FVIII inhibitor: before injection
- **Body weight** before injection
- **Vital signs** before injection as well as 1 and 72 hours after the end of injection
- **Information in the patient diary** (if applicable) will be reviewed by the Investigator. For this purpose, the patient diaries will be collected and the data from completed diary pages transcribed to the eCRF.
- IMP for home treatment will be given to patients. They will be re-supplied whenever necessary during the study.

Table 3 Flow Chart of Assessments of Initial PK Visit[1]

	Before injection (within 1 hour)	0.5 h ±5 min	1 h ±5 min	3 h ±15 min	6 h ±30 min	9 h ±1 h	24 h ±2 h	30 h ±2 h	48 h ±2 h	72 h ±2 h
FVIII:C plasma concentration[2]	x	x	x	x	x	x	x	x	x	x
VWFAg	x									
FVIII inhibitor	x									
Body weight	x									
Vital signs[3]	x		x							x
AE monitoring	Throughout observation period									

[1] After washout period of ≥ 96 h after last FVIII administration. A washout period of at least 72 hours would be acceptable only if a patient is at a high risk of bleeding .

[2] One-stage and chromogenic assays.

* For PK analyses, data from the one-stage assay will be used (see Section 4.1 and Section 6.4.3).

[3] Systolic and diastolic blood pressure, body temperature, pulse.

7.2.3 Prophylactic Treatment—Phase I, including End-of-Phase-I Visit

The 72-hour sampling time point of the Initial PK Visit marks the beginning of Prophylactic Treatment—Phase I, in which patients will be treated prophylactically every other day or 3x/week with a dose of 30–40 IU/kg BW for about 1–3 months until PK data have been analysed and discussed with the investigator.

Dose escalations are allowed in case of an inadequate frequency and severity of breakthrough bleeding episodes in accordance with the institution's standard clinical care.

The maximum dose for a single infusion in Prophylaxis Treatment Phase I is 45 IU/kg BW.

Throughout Prophylactic Treatment—Phase I, visits will take place according to the following schedule:

Day 14 Visit: will take place 14-21 days after the administration of the first dose of *Human-cl rhFVIII* on initial PK Visit day 1.

Day 30 Visit: will take place 30 days (± 3 days) after the administration of the first dose of *Human-cl rhFVIII* on initial PK Visit day 1.

A blood sample will be taken for FVIII inhibitor testing. Blood draw for inhibitor testing should be performed, preferably, when FVIII level has reached baseline.

End-of-Phase-I Visit

At the end of Prophylactic Treatment—Phase I, the prophylactic dose and dosing interval will be determined for each patient based on the analysis of individual PK data as described in Section 6.4.3. A blood sample will be taken for FVIII inhibitor testing during this visit, only if the End-of-Phase I Visit does not coincide with the Day 30 Visit. The End-of-Phase-I Visit marks the beginning of Prophylactic Treatment—Phase II, in which patients will be treated prophylactically for 6 months using the dose and dosing interval determined during the End-of-Phase-I Visit as described in Section 6.4.3.

7.2.4 Prophylactic Treatment—Phase II

Throughout the Prophylactic Treatment—Phase II, visits will take place every 2 months.

2-Month Visit (± 1 week) in Phase II

The 2-Month Visit will take place 2 months after the start of Prophylactic Treatment—Phase II.

Note: To allow the patient's true trough levels to be determined, patients should be advised to present for blood sampling at the end of a regular treatment interval, i.e., *within 3 hours before injection of the next scheduled dose*.

The following assessments will be performed:

- **Blood samples** for the determination of FVIII:C trough levels (one-stage and chromogenic assays) and FVIII inhibitor will be taken *within 3 hours before injection of the next scheduled FVIII dose*. Whenever an extra dose of FVIII has to be administered between scheduled prophylactic doses (e.g., for on-demand treatment of a bleeding episode), blood sampling for the determination of FVIII:C trough levels has to be delayed until the end of the next regular treatment interval.
- **Information in the patient diary** will be reviewed by the Investigator. For this purpose, the patient diaries will be collected and the data from completed diary pages transcribed to the eCRF.

4-Month Visit (± 1 week) in Phase II

The 4-Month Visit will take place 4 months after the start of Prophylactic Treatment—Phase II. The assessments performed will be identical to those performed at the 2-Month Visit in Phase II.

The dose per injection may be reduced for the remainder of the study provided that FVIII:C trough levels (one-stage assay) obtained at the 2-Month Visit were ≥ 0.01 IU/mL and the patient has not experienced any spontaneous bleed up to the 4-Month Visit.

7.2.5 Monthly Compliance Checks

Patient compliance will be closely monitored by the investigator or authorised study personnel on the basis of patient diaries and monthly compliance checks.

For information on the use of patient diaries, refer to Section 6.7.2.

During Prophylactic Treatment—Phases I and II, monthly compliance checks (± 1 week) will be performed by telephone or during personal visits by the patient. The 1 month compliance check in Phase-I will be combined with the Day 30 Visit. During these checks,

the investigator will determine whether the patient has adhered to the prescribed dose and dosing interval and whether the dose and dosing interval are adequate.

7.2.6 Study Completion Visit

The Study Completion Visit will take place 6 months (± 1 week) after the beginning of Prophylactic Treatment—Phase II.

Note: To allow the patient's true trough levels to be determined, patients should be advised to present for blood sampling at the end of a regular treatment interval, i.e., *within 3 hours before injection of the next scheduled dose*.

The following assessments will be performed:

- **Blood samples** will be taken:
  - FVIII:C plasma concentration (one-stage and chromogenic assays) for the determination of trough levels will be taken *within 3 hours before injection of the next scheduled FVIII dose*. Whenever an extra dose of FVIII has to be administered between scheduled prophylactic doses (e.g., for on-demand treatment of a bleeding episode), blood sampling for the determination of FVIII:C trough levels has to be delayed until the end of the next regular treatment interval. The next scheduled FVIII dose will no longer be considered study treatment.
  - FVIII inhibitor
- **Physical examination**
- **Information in the patient diary** will be reviewed by the Investigator. For this purpose, the patient diaries will be collected and the data from completed diary pages transcribed to the eCRF.

All used and unused IMP vials will be returned to site.

If patients continue treatment in the "Sub-Study Extension Phase" after the completion visit, the completion visit data will also be used as the screening data for the "Sub-Study Extension Phase". If possible both visits should occur on the same day.

7.2.7 Unscheduled Visits

In case of positive inhibitor results, inhibitor retesting using a second, separately drawn sample should be performed, preferably within 15 days of becoming aware of the positive result. Other reasons for unscheduled visits may be the occurrence of serious AEs or hospitalizations due to severe BEs or surgical interventions.

The data that will be documented during BE or surgical visits are given in Sections 8.2.1 and 8.2.3.

7.2.8 Study visits of "Sub-Study Extension Phase"

7.2.8.1 Screening Visit

Patients have to be informed about the "Sub-Study Extension Phase" details and have to give their written informed consent before any investigations and assessments can be performed. The screening visit should be performed in conjunction with the study completion visit of the GENA-21b study. All test results that coincide with the study completion visit of GENA-21b, will be used for the screening visit of the "Sub-Study Extension Phase".

The following information will be documented/assessed in addition:

- Check of inclusion- and exclusion criteria
- Body weight

The Investigator will hand out a patient diary and instruct the patients on how to document details of treatment with *Human-cl rhFVIII*, bleeds, AEs and concomitant medication.

IMP for home treatment will be given to patients. They will be re-supplied whenever necessary during the "Sub-Study Extension Phase".

7.2.8.2 6-monthly (± 2 weeks) Follow Up Visits

The 6-monthly follow up visit will take place every 6 months after the completion of Prophylactic Treatment—Phase II and the screening for the "Sub-Study Extension Phase".

The following assessments will be performed:

- **Blood samples** for the determination of FVIII:C trough levels (one-stage and chromogenic assays) and FVIII inhibitor will be taken *within 3 hours before injection of the next scheduled FVIII dose*. Whenever an extra dose of FVIII has to be administered between scheduled prophylactic doses (e.g., for on-demand treatment of a bleeding episode), blood sampling for the determination of FVIII:C trough levels and inhibitor has to be delayed until the end of the next regular treatment interval.

- **Information in the patient diary** will be reviewed by the Investigator. For this purpose, the patient diaries will be collected and the data from completed diary pages transcribed to the eCRF.

During these visits, the investigator will determine whether the patient has adhered to the prescribed dose and dosing interval and whether the dose and dosing interval are adequate.

Note: To allow the patient's true trough levels to be determined, patients should be advised to present for blood sampling at the end of a regular treatment interval, i.e., *within 3 hours before injection of the next scheduled dose*.

7.2.8.3 Study Completion Visit

The study completion visit is planned to take place within the 4th quarter of 2020.

The following assessments will be performed:

- **Blood samples** will be taken:
  - FVIII:C plasma concentration (one-stage and chromogenic assays) for the determination of trough levels and inhibitor will be taken *within 3 hours before injection of the next scheduled FVIII dose*. Whenever an extra dose of FVIII has to be administered between scheduled prophylactic doses (e.g., for on-demand treatment of a bleeding episode), blood sampling for the determination of FVIII:C trough levels and inhibitor has to be delayed until the end of the next regular treatment interval.
- **Physical examination**
- **Body weight**
- **Information in the patient diary** will be reviewed by the Investigator. For this purpose, the patient diaries will be collected and the data from completed diary pages transcribed to the eCRF.

  All used and unused IMP vials will be returned to site.

7.2.8.4 Unscheduled visit

For Unscheduled visits during the "Sub-Study Extension Phase" see section 7.2.7

7.3 Study Duration

7.3.1 Planned Duration for an Individual Patient

The study duration for each patient will be approximately 7–9 months in the GENA-21b study.

The duration of the "Sub-Study Extension Phase" for each patient will be approximately between 2.5 and 3.5 years depending upon the completion date of the GENA-21b study. The first patient in Japan completed Prophylactic Treatment-Phase II in June 2017 and the last patient completed Prophylactic Treatment-Phase II in September 2018. The clinical study end of the "Sub-Study Extension Phase" is planned to be in the 4th Quarter of 2020. Thus, individual study duration may vary from approximately 2.5 to 3.5 years.

The overall study duration from start of the GENA-21b in the 2nd Quarter of 2015 until "Sub-Study Extension Phase" completion visit in the 4th Quarter of 2020 is approximately 5.75 years.

7.3.2 Planned Duration for the Study as a Whole

This study started in the 2nd Quarter 2015, and the end of the GENA-21b study was in the 3rd Quarter 2018, resulting in an overall study duration of about 3 years.

The GENA-21b study was considered clinically completed when the last patient underwent the Study Completion Visit.

The study start of the "Sub-Study Extension Phase" was in July 2017 and is planned to be completed in the 4th Quarter of 2020 with total study duration of about 3.5 years. The "Sub-Study Extension Phase" will be considered completed when the last patient has undergone the Study Completion Visit for the "Sub-Study Extension Phase".

The overall study duration from start of the GENA-21b in the 2nd Quarter of 2015 until "Sub-Study Extension Phase" completion visit in the 4th Quarter of 2020 is approximately 5.75 years.

7.3.3 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 procedures will be arranged on an individual study 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.

Furthermore, the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will promptly be informed of the premature termination of the study and will be provided with a detailed written explanation. The pertinent regulatory authorities should be informed in accordance with national regulations.

Early termination of the study as a whole or by study centre may occur for the following reasons:

Clinical Study

The study as a whole will be terminated prematurely as soon as new toxicological or pharmacological findings or SAEs invalidate the earlier positive benefit-risk-assessment.

Study Centre

The study can be terminated at any time at an individual centre if:

- The centre cannot comply with the requirements of the protocol.
- The centre cannot comply with GCP standards.
- The required recruitment rate cannot be met.

Should the study be prematurely terminated, all study materials (e.g., blank diaries, IMPs etc.) must be returned to the Sponsor.

8 ASSESSMENTS AND METHODS

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

8.1 Baseline Information

The patient's baseline data (see Section 7.2.1) will be obtained by interviewing the patient, evaluating the patient's medical record, and performing a physical examination and relevant laboratory tests.

8.2 Efficacy Assessments

8.2.1 Bleeding Episodes (BEs)

BE data to be documented

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

- BE type (spontaneous, traumatic, postoperative, other)
- BE site
- BE severity (minor, moderate, major, life-threatening)
- Date and time the BE first occurred or was first noticed
- Date and time the BE ended
- Dates and times the IMP was injected
- IMP dose(s) and batch number(s)
- Assessment of the efficacy of treatment at the end of the BE; see item (c) below

All of these parameters will be documented by the patient (together with the investigator in case of on-site treatments) in the patient diary. Patients who experience a major or life-threatening BE should be treated at the study site.

a) Definition of BE

If the treatment of a BE at one site is interrupted for more than 48 hours, the events are recorded as two separate BEs; if another than the original bleeding site is affected, the events are recorded as separate BEs at any time.

If there are several simultaneous bleeding sites, each bleeding site is recorded as a separate BE.

For certain major bleeding events, e.g., iliopsoas bleeds or bleeding into target joints, it may be necessary to continue treatment beyond the resolution of the acute phase to prevent recurrent haemorrhage. These additional injections should be recorded in the diary (and eCRF) but will not be evaluated as treatments of the BE.

b) Assessment of the severity of a BE

The following categorisation guide for severity of bleeding episodes is included in patient diary:

- **Minor:** A bleeding that just starts and has little symptoms. For example: early onset muscle and joint bleeds with no visible symptoms such as little or no change in the range of motion of affected joint (if joint bleeding event); mild restriction of mobility and activity, scrapes, superficial cuts, bruises, superficial mouth bleeds and most nose bleeds.
- **Moderate:** A bleeding that involves swelling or pain including some decrease in range of motion of affected joint (if joint bleeding event) or moderate decrease in mobility and activity. For example: advanced soft tissue and muscle bleeds into the limbs, bleeding into the joint space, such as the elbow, knee, ankle, wrist, shoulder, hip, foot or finger.
- **Major:** A bleeding that causes significant pain, substantial decrease in range of motion of affected joint (if joint bleeding event), incapacity. For example: complicated joint bleeds, bleeds of the pelvic muscles, eyes.
- **Life-threatening:** Bleedings in the cranium (skull), abdomen, digestive system or chest, central nervous system bleeds, bleedings in the area of the neck or throat or pharynx, head or other major trauma.

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

At the end of a BE, treatment efficacy will be assessed by the patient (together with the investigator in case of on-site treatment) using the following predefined criteria:

- **Excellent:** Abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single injection
- **Good:** Definite pain relief and/or improvement in signs of bleeding within approximately 8–12 hours after an injection, requiring up to 2 injections for complete resolution
- **Moderate:** Probable or slight beneficial effect within approximately 12 hours after the first injection, requiring more than 2 injections for complete resolution

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

The proportion of BEs **successfully treated** with IMP will be evaluated for all BEs together and by severity. All efficacy ratings assessed as either 'excellent' or 'good' will be considered 'successfully treated'.

8.2.2 Efficacy Assessment of prophylaxis treatment in the "Sub-Study Extension Phase"

The efficacy of *Human-cl rhFVIII* in the prophylactic treatment will be assessed based on the frequency of total and 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.

8.2.3 Surgical Prophylaxis

For any surgical procedure performed during the GENA-21b study and the "Sub-Study Extension Phase", the following data will be recorded:

- Body weight within 12 hours before start of the surgery
- Type of surgery (planned or emergency)
- Location of surgery
- Severity of surgery (minor, major); see item a) below
- Expected duration of surgery
- Actual duration of surgery (start and end times, i.e., skin to skin).
- Details on dose(s) of *Human-cl rhFVIII* given pre-, intra-, or postoperatively; see item b) below
- Pre-(within 3h before start of the surgery), intra-, and postoperative FVIII plasma levels; see item c) below
- Expected and actual blood loss; see item d) below
- Presence of wound haematomas and whether or not they require surgical evacuation
- Safety lab tests (haematology, chemistry: within 12 hours before start of the surgery and 24 hours after the end of surgery)
- Vital signs within 12 hours before start of the surgery (before blood sample collection)
- Narrative describing the outcome and efficacy of the intervention
- Efficacy assessment at the end of surgery by surgeon
- Efficacy assessment at the end of the post-operative period by haematologist
- Overall efficacy assessment at the end of surgical prophylaxis by the surgeon and the haematologist; see item e) below
- Details on concomitantly administered products, including any blood or blood product transfusions but excluding drugs given for routine anaesthesia
- Monitoring of AEs
- Inhibitor test (central laboratory) with plasma sample obtained within 3 to 8 weeks after the end of the surgery. This visit can coincide with any other study visit where inhibitor testing is scheduled.

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

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

- The **end of the postoperative period** is the time the patient returns to his regular FVIII treatment regimen.

a) Severity of surgery

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

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

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

b) Pre-, intra-, and postoperative doses of Human-cl rhFVIII

Details on the pre-, intra-, and postoperative administration of *Human-cl rhFVIII* will be recorded and include the dates and times of administration as well as the batch numbers.

In this study, only bolus injection is allowed. Continuous infusions are prohibited.

c) FVIII plasma levels

FVIII plasma levels will be documented for the following time points:

- Immediately (≤ 30 min) before and 30 ± 15 min after preoperative injection of IMP
- Immediately (≤ 30 min) before and 30 ± 15 min after each intraoperative bolus dose, if any
- Immediately (≤ 30 min) before and 30 ± 15 min after each postoperative dose, if any; in case of major surgery, the determination of FVIII plasma levels is mandatory for the first 3 postoperative doses

FVIII:C activity will be assessed at the local laboratory. In addition, samples will be shipped to the central laboratory for one-stage and chromogenic assay assessments (see Section 8.4).

d) Estimated and actual blood loss

Before surgery, the surgeon will provide written estimates of both the **average** and **maximum volume (mL) of expected blood loss** for the planned surgical procedure for a patient with normal haemostasis of the same sex, age, and stature as the patient enrolled in

this study. After surgery, the surgeon will estimate the **actual blood loss** experienced by the patient.

e) Assessment of the efficacy of surgical prophylaxis

Efficacy will be assessed at the end of surgery by the surgeon and at end of the postoperative period by the haematologist. In both cases, predefined assessment criteria will be used. In addition, there will be an overall assessment of efficacy jointly made by the surgeon and the haematologist without predefined assessment criteria.

At the end of surgery (by surgeon)

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

At the end of the postoperative period (by haematologist)

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

Overall efficacy assessment at the end of the postoperative period (by surgeon and haematologist)

An overall efficacy assessment using the 'excellent,' 'good,' moderate,' and 'none' scale (without any predefined criteria) taking both the intra- and postoperative assessment into account will be done jointly by the surgeon and the haematologist.

Based on this overall efficacy assessment, all efficacy ratings assessed as either 'excellent' or 'good' will be considered 'successfully treated'.

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

	Within 12 hours before start	Within 3 hours before start	Surgery		POP day 1	Any POP day	At the end of POP period[b]	3-8 weeks after surgery*
			Intra-operatively	End[a]				
Body weight	x							
Type of surgery	x							
Location of surgery	x							
Severity of surgery	x							
Expected duration of surgery	x							
Expected average and maximum blood loss during surgery	x							
Actual duration of surgery				x				
Actual blood loss during surgery				x				
Administration of *Human-cl rhFVIII*		x	(x)	(x)	(x)	(x)	(x)	
FVIII plasma levels		#	(#)	(#)	#[c]	#	#	
Presence of wound haematomas					x	x	x	
Safety lab tests	x				(x)	(x)	(x)	
Vital signs	x		x		x			
Efficacy assessment				S			H	
Overall efficacy assessment							SH	
FVIII Inhibitor								**x**
Narrative of outcome							x	
Concomitant medications	throughout observation period							
AE monitoring	throughout observation period							

POP, postoperative; ( ) optional; # samples to be taken before (≤ 30 min) and 30 ± 15 min after IMP administration

[a] time immediately after the last surgical suture.

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

[c] in case of major surgery, the determination of FVIII plasma levels is mandatory for the first 3 postoperative doses

S, performed by surgeon; H, performed by haematologist; SH performed by surgeon and haematologist

8.3 Safety Assessments

8.3.1 Safety Endpoints

Any of the following drug safety information shall be collected:

- Adverse events (AEs) and serious adverse events (SAEs) temporally associated with the administration of IMP (definitions and reporting requirements see Section 8.3.2)
- Other relevant safety information, including post-study safety reports, instances of drug overdose, drug-drug interactions, abuse, misuse, medication error, or lack of efficacy (see Section 8.3.5)

8.3.2 Adverse Events

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. "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:** 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 has resolved or until the medical condition of the patient has stabilized. Any follow-up information collected will be made available to the Sponsor.

Collection of AEs

The condition of the patient will be monitored throughout the study. At each scheduled or unscheduled study visit and at each monthly compliance check, AEs will be elicited using a standard non-leading question such as "How have you been since the last visit?". In addition, the patient diaries will be checked by the investigator for any documented event.

Any AE or ADR which occurs during the study will be documented in detail on the appropriate pages of the eCRF. If the patient reports several signs or symptoms representing a single syndrome or diagnosis, the syndrome or diagnosis should be recorded in the eCRF. The investigator responsible will grade the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (non-serious or serious), and the causality as defined below. The Sponsor is responsible for assessing the expectedness of each ADR (expected or unexpected) as defined below.

In the event of clinically significant abnormal laboratory findings, the tests will be repeated and the patient followed up until the laboratory values have returned to normal and/or an adequate explanation for the abnormality has become available.

Diseases, signs, and symptoms and/or laboratory abnormalities already present before the first administration of IMP will not be considered AEs unless an exacerbation in intensity or frequency (worsening) occurs.

The responsible investigator will provide detailed information about any abnormalities and about the nature of and reasons for any action taken as well as any observations or comments that may be useful for the interpretation and understanding of an AEs or ADR.

Severity of AEs

The severity of 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.

The grading of AEs is up to the medical judgement of the investigator and will be decided on a case-by-case basis.

Causality of AEs

The relationship of AEs to the administered IMP will be assessed by the responsible investigator. The causality of AEs will be classified as follows:

- **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 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.

Outcome of AEs

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

(a) Recovered, resolved
(b) Recovering, resolving
(c) Not recovered, not resolved
(d) Recovered, resolved with sequelae
(e) Fatal
(f) Unknown

A patient's **death** per se is not an event, but an outcome. The event having resulted in the patient's death must be fully documented and reported. Deaths occurring within 4 weeks after IMP treatment end also have to be reported, regardless of whether or not they are considered treatment-related.

Action(s) taken

AEs requiring action or therapy must be treated with recognised standards of medical care to safeguard 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:

- General actions taken in the event of an AE
  - None
  - Medication (other than IMP) or other (e.g., physical) therapy started
  - Test performed
  - Other (to be specified)
- IMP-related actions taken in the event of an AE
  - None
  - Product withdrawn
  - Dose reduced
  - Dose increased

The responsible investigator will follow up on each AE until it has resolved or until the medical condition of the patient has stabilised. Any relevant follow-up information will be reported to the Sponsor.

8.3.3 Serious Adverse Events (SAEs)

A **serious** AE (SAE) is any untoward medical occurrence that at any dose:

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

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 may hypothetically have caused the death of the patient if it had been more severe.

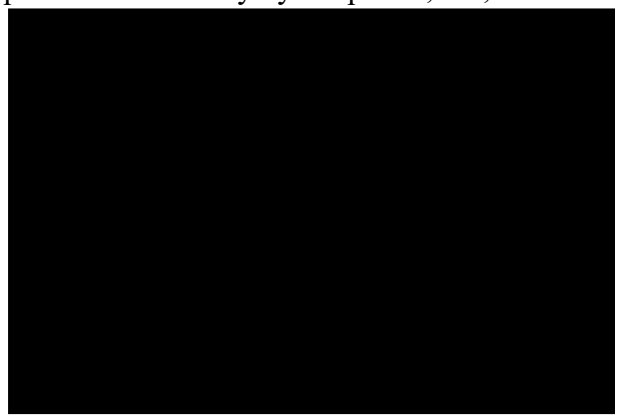
In deciding whether a **medical event is important** enough to be considered a serious AE/ADR, medical judgment should be exercised. Thus, any event that is not immediately life-threatening or does not result in death or hospitalization but may jeopardise the health of the patient or require an intervention to prevent one of the other outcomes listed in the definitions above, should be considered 'serious'.

One such 'important medical event' is the **development of FVIII inhibitors**. Another is the **suspected transmission of an infectious agent.** These events, therefore, **have to be reported as SAEs**.

A suspected virus transmission means that virus antigen has been detected in the patient. The passive transmission of antibodies alone does not constitute a suspected virus transmission.

8.3.4 SAE Reporting Timelines

All SAEs, whether or not they are suspected to be related to the study treatment, are to be reported immediately by telephone, fax, or email to the Clinical Project Manager:



Within 24 hours after recognition of the event, an Octapharma 'Serious Adverse Event Report' must be completed and submitted. All SAEs should be reported to:

Exemption from the SAE reporting requirement

Exemptions from the SAE reporting requirement include surgeries that are elective or planned and prolongations of existing hospitalizations for economic or social rather than medical reasons. Such surgeries or prolongations of hospitalizations should not be considered SAEs.

8.3.5 Other Relevant Safety Information

Instances of drug overdose, drug-drug interactions, abuse, misuse, medication error, or lack of efficacy (items b) to g)) should be reported as AEs or SAEs, as applicable.

a) Post-study safety reports

The investigator should also report any ADR (i.e., any AE with a suspected causal relationship to the IMP) occurring after completion of the study. The usual procedure for reporting post-marketing safety information should be followed, but the suspected causal relationship to the clinical study should be stated on the report.

Deaths occurring within 4 weeks after IMP treatment end also have to be reported, regardless of whether or not they are considered treatment-related.

b) Drug overdose

An overdose is the 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 it must be of clinical relevance. The event must be clearly identified as an overdose.

c) Drug-drug interactions

A drug interaction is a situation where a substance/medicinal product affects the activity of an IMP, i.e. increases or decreases the effect(s) of an IMP, or produces an effect that none of the products would exhibit on their own. The event must be clearly identified as resulting from a drug-drug interaction.

d) Abuse

Abuse is the deliberate use of a medicinal product that may lead to addiction accompanied by harmful physical or psychological effects.

e) 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.

f) 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.

g) Lack of efficacy

Lack of efficacy is suspected when the therapeutic result is not as expected, e.g., when patients with haemophilia experience continued bleeding despite the correct administration of coagulation factors.

8.4 Laboratory Assessments

The **routine safety laboratory tests** (as well as any FVIII:C measurements in case of surgery that may become necessary) will be done by the local laboratory.

FVIII:C (one-stage and chromogenic assays), **FVIII inhibitors**, and **VWFAg** will be assessed by the following central laboratory:

Colorado Coagulation

Esoterix Inc.

8490 Upland Drive, Suite 100
Englewood, CO 80112, USA

In surgical prophylaxis (see Section 8.2.3), FVIII:C activity will be assessed at the local laboratory. In addition, samples will be shipped to the central laboratory for one-stage and chromogenic assay assessments.

Inhibitor activity will be determined by the modified Bethesda assay (Nijmegen modification) using congenital FVIII-deficient human plasma spiked with *Human-cl rhFVIII* as a test base. Inhibitor tests will be performed before the first injection of *Human-cl rhFVIII,* on Day 14 and Day 30 after the administration of the first dose of *Human-cl rhFVIII*, at the End-of-Phase-I Visit (this may coincide with Day 30 Visit), at the Phase II 2-Month Visit and 4-Month Visit, at the Study Completion Visit, every 6 months during the "Sub-Study Extension Phase", at Sub-Study completion visit, and whenever inhibitor development is suspected. Blood draw for inhibitor testing should be performed, preferably, when FVIII level has reached baseline. In case of positive inhibitor results, inhibitor retesting using a second, separately drawn sample should be performed, preferably within 15 days of becoming aware of the positive result.

8.5 Appropriateness of Measurements

The criteria for assessing the efficacy of *Human-cl rhFVIII* in the treatment of BEs as well as in surgical prophylaxis are identical to those in the preceding studies with *Human-cl rhFVIII*, thus facilitating adequate comparison of results across studies.

The measurements of the essential tolerability and immunogenicity parameters of *Human-cl rhFVIII* are identical to those used in the preceding studies with *Human-cl rhFVIII*. In

particular, inhibitor measurements are performed by a central laboratory using validated assays.

9 DATA HANDLING AND RECORD KEEPING

9.1 Documentation of Data

9.1.1 Source Data and Records

Source data are defined as 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 eCRF must be supported by source data in the patient records, with exceptions listed in Section 9.1.2.

The investigator will permit study-related monitoring, audit(s), IEC review(s) and regulatory inspection(s) by providing direct access to source data and records.

The investigator may authorise site staff (e.g., sub-investigators, nurses) to enter study data into the eCRF. This must be documented in the 'Delegation of Authority Log,' which is to be filled in and signed by the responsible investigator.

9.1.2 Case Report Forms

For each patient enrolled, an electronic CRF (eCRF) will be completed within the Electronic Data Capture (EDC) system and approved by the investigator or an authorised sub-investigator. Monitors must provide a SDV flag to each of the eCRF pages in addition to the approval flag by the investigator.

Study site staff (e.g., research nurse) will be responsible for entering all patient data into the validated EDC system. All site personnel will be trained on the EDC system and study-specific eCRFs prior to receiving access to the live database for data entry, as defined in applicable SOPs. The site is also provided with the approved eCRF Completion Guidelines which will assist in data entry and data issues/questions. The site will be notified once the database is active to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must appear on the delegation of authority log.

If any errors in the eCRFs are found during the data review process, discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either a monitor or Data Management. The programmed checks fire automatically once an eCRF page is saved within the system. The output of the programmed checks are referred to as 'discrepancies'. Discrepancies are generated by the input of illogical eCRF data. The purpose of these objects is to clarify the use, context, or insertion of illogical or missing data with the site or designee.

All discrepancies (programmed and manual) will be submitted to the site personnel or monitor for the site within the EDC system. Once the site responds to a discrepancy, Data Management or the monitor will review the new or changed data to ensure an appropriate response and close the discrepancy within the system.

9.1.3 Changes to eCRF Data

Errors occurring on the EDC system can only be corrected by the investigator(s) or designated site personnel. An audit trail documents all changes to the data over the entire study period. If data is changed as a result of a query, a comment must be supplied within the query text, stating the reason for the change, prior to closing. The study monitor should provide guidance to investigators and the investigators' designated representatives on making such corrections. In addition, any changes to a previously saved eCRF page that has not had a query generated will need to have a reason specified for the data change. This is handled within the EDC system, and relevant prompts appear once any changes are made.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management for incomplete or ambiguous resolutions. If the query response provided confirms the data as correct, the discrepancy will be closed based on the query response. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks are performed and programs are run throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the investigator prior to database lock.

9.2 Information Provided to Investigators

An Investigator's Brochure (IB) will be provided to the investigators before the start of the study. The IB 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 IB will be updated by the Sponsor at regular intervals or whenever new information about the IMP becomes available. The investigators will be informed about the methods for rating relevant study outcomes and for completing eCRFs 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.

9.3 Responsibilities

The investigator is accountable for the conduct of the clinical study. If any responsibilities are delegated, the investigator should maintain a list of appropriately qualified persons to whom he or she has delegated significant study-related duties.

A 'Delegation of Authority Log' will be filled in and signed by the responsible investigator. Study site staff (e.g., sub-investigators, nurses) listed in the log will be authorised to perform study-related tasks and to enter specific data into the eCRF.

9.4 Investigator 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, 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 eCRF 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.

9.5 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 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.

10 STATISTICAL METHODS AND SAMPLE SIZE

The statistical analysis will be delegated under an agreement of transfer of responsibilities to an external Contract Research Organization (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.

A 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.

The data collected in the GENA-21b and the "Sub-Study Extension Phase" will be stored in 2 separate databases and analysed separately.

10.1 Determination of Sample Size

10.1.1 Power

With 50 patients with 6 months of treatment (300 person-months), one can show that the bleeding rate over all prophylactically treated patients (primary efficacy endpoint) is less than 29 per patient per year (α=0.0125 one-sided; adjusted for 2 multiple tests), assuming that BEs constitute a non-frequent event following a Poisson distribution and that the true bleeding rate is:

- 2.3 per patient per year or lower with a power of > 99% (Scenario 1)
- 6.7 per patient per year or lower with a power of > 99% (Scenario 2)
- 13 per patient per year or lower with a power of > 99% (Scenario 3)

An additional assumption for this statistical analysis is that the BEs occur at the same frequency independent from individual patients.

Assuming that 20 patients will be treated with a 2x/week or less frequent prophylactic regimen, one can show that the bleeding rate over all patients treated with such a dosage regimen (secondary efficacy endpoint) is less than 29 per patient per year (α=0.0125 one sided; adjusted for 2 multiple tests), assuming that BEs constitute a non-frequent event following a Poisson distribution and that the true bleeding rate is:

- 2.3 per patient per year or lower with a power of > 99% (Scenario 1)
- 6.7 per patient per year or lower with a power of > 99% (Scenario 2)
- 13 per patient per year or lower with a power of > 99% (Scenario 3)

Scenario 1 assumes that the annualised bleeding rate equals the estimated mean annual bleeding rate in the GENA-08 trial
Scenario 2 assumes that the annualised bleeding rate equals the upper 2-sided 95% CI of study GENA-09 (i.e., 12*0.554)
Scenario 3 assumes that the annualised bleeding rate equals 2 times the upper 2-sided 95% CI of study GENA-09

For the "Sub-Study Extension Phase", no inferential analysis including formal hypothesis testing is planned. The patients are offered to continue treatment after the completion of the GENA-21b evaluation study in accordance with the study protocol. Thus, neither formal sample size estimation nor power calculation is considered.

10.1.2 Method of power calculation

Assuming that the total number of BEs in 6 months in n patients is Poisson-distributed with $\lambda_{\text{half year}} = n \times 0.5 \times \lambda_{\text{year}}$, where $\lambda_{\text{half year}}$ is the expected number of BEs per 6 months for all patients and λ_{year} is the expected individual bleeding frequency per year, the critical value c for the Poisson test is calculated as the last number before the first number for which the cumulative distribution function for the Poisson distribution with mean $\lambda_{\text{half year},0} = n \times 0.5 \times 29$ (null hypothesis $\lambda_{\text{year}} \geq 29$) is above α, the predefined nominal type I error. The power for this situation assuming $\lambda_{\text{half year},1} = n \times 0.5 \times \lambda_{\text{year},1}$ with a $\lambda_{\text{year},1} < 29$ (alternative hypothesis) is then calculated as the value of the cumulative distribution function for the Poisson distribution with mean $\lambda_{\text{half year},1}$ at the critical value c.

10.2 Populations for Analysis

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

- **Safety analysis population:**
  All patients who received at least one dose of *Human-cl rhFVIII*
- **Intent-to-Treat (ITT) analysis population:**
  All patients in the safety analysis population for whom any data was collected after treatment with *Human-cl rhFVIII*
- **Efficacy Per Protocol (PP) analysis population:**
  All patients 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 patients will be excluded from this population:

- Patients who violate the following inclusion criteria:
  - Severe haemophilia A (FVIII:C <1%; according to medical history records)
- Patients who fulfil the following exclusion criteria:
  - Other coagulation disorder than haemophilia A
  - Present or past FVIII inhibitor activity (≥ 0.6 BU),
  - Severe liver or kidney disease (ALT and AST levels > 5 times of upper limit of normal, creatinine >120 µmol/L),
- Patients significantly noncompliant with the protocol, e.g., noncompliance in adequately completing the patient diary
- Patients with dosing or treatment errors, e.g., the use of other FVIII products (except for emergencies as mentioned in Section 5.3.2) or several *unexplained* and significant deviations from the recommended dose regimen and/or dosing frequency

- **PK analysis population:**
  All patients in the ITT population who started the initial PK assessment with *Human-cl rhFVIII*.

- **PK-PP analysis population:**
  All patients in the PK analysis population who completed the initial PK sampling phase of the trial without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results:
  Especially the following patients will be excluded from this population:
  - Patients who violate the following inclusion criteria:
    - Severe haemophilia A (FVIII:C <1%; according to medical history records)
  - Patients who fulfil the following exclusion criteria:
    - Coagulation disorder other than haemophilia A
    - Present or past FVIII inhibitor activity (≥ 0.6 BU),
    - Severe liver or kidney disease (ALT and AST levels > 5 times of upper limit of normal, creatinine > 120 µmol/L)
  - Patients who use concomitant medication before or during the PK phase that may confound study results.
  - Patients who use FVIII treatment that may confound the PK results: resulting in baseline FVIII:C level ≥ 0.15 IU/mL
  - Patients who receive less than 80% or more than 120% of the planned dose
  - More than 2 consecutive blood samples missing for PK assessment

  - More than 3 post-baseline blood samples missing for PK assessment

- **Population of patients on individual prophylactic treatment schedule (PROPH):** All patients in the ITT population who enter the Prophylactic Treatment—Phase II of the study (i.e., have at least one prophylactic treatment in Phase II)

- **PP population of patients on prophylactic treatment schedules (PROPH-PP):**
  All patients in the PP population who enter the Prophylactic Treatment—Phase II of the study
  - who have evaluable initial PK results for the evaluation of the individual prophylactic treatment schedule
  - with at least 6 months (–2 weeks) of individual prophylactic treatment (Prophylactic Treatment—Phase II) with *Human-cl rhFVIII*
  - who have no significant dosing or treatment errors, e.g., several unexplained interruptions of individual prophylaxis with *Human-cl rhFVIII*, e.g., > 20% of prophylactic injections were not given within the prescribed treatment intervals (± 1 day)
- **Subpopulations of the PROPH populations:**
  (1) patients with 2x/week (or less) individual prophylaxis in Prophylactic Treatment—Phase II (defined as patients on a 2x/week (or less) treatment schedule 80% of the time and without a decrease in the treatment interval in the last defined treatment schedule as compared to the previous one).
  (2) patients with more than 2x/week individual prophylaxis in Prophylactic Treatment—Phase II (all patients in the PROPH population who are not in subpopulation (1)).
- **Population of treated BEs (BLEED):**
  All documented bleeds of patients in the ITT population for which
  - any amount of treatment with *Human-cl rhFVIII* is documented and which
  - starts between the start of Prophylactic Treatment—Phase I and the Study Completion Visit (or withdrawal)
- **PP population of treated BEs (BLEED-PP):**
  All documented bleeds in the BLEED population of patients in the PP population for which no other FVIII product was documented.

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

The PROPH population is considered primary for analysis of efficacy data on prophylaxis; the BLEED population is considered primary for analysis of efficacy data on BEs.

To evaluate the robustness of the study results, efficacy analyses will also be done on basis of the respective PP populations. The PK-PP population is the primary analysis population for the PK data; however, any effort will be made to derive a calculation for the individual prophylactic scheme from the initial PK for all patients who start prophylaxis.

The analysis of safety will be based on the safety analysis population.

For a detailed description of patients included in the "Sub-Study Extension Phase", the following population flags will be used:

- 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 fulfill the following exclusion criteria:
    - other FVIII product than *Human-cl rhFVIII* was received between completion visit of GENA-21b and start of "Sub-Study Extension Phase" (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.
- Population of subjects on prophylactic treatment schedule (PROPH): All subjects in the ITT population who have at least one prophylactic treatment
- Per-protocol population of subjects on prophylactic treatment schedules (PROPH-PP): 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*
- Population of bleedings (BLEED): 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 product 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 product 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.

Due to the limited sample size of patients in the "Sub-Study Extension Phase" the population flags will be used to describe patient characteristics in more detail within patient profiles or subject data listings. No subgroup analyses by use of these populations are planned. In case of extreme data constellations sensitivity analyses by excluding patients from the analysis or by focusing the analysis on patient populations as described above can be performed, if deemed reasonable with respect to sample size.

10.3 Efficacy Analysis Plan

10.3.1 Primary Objective

The primary objective of this study is to compare the annualised total bleeding rate of individually tailored prophylaxis with the historical bleeding rate observed in patients having received on-demand treatment with **Human-cl rhFVIII** *from study GENA-01.*

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

a) Primary analysis

Hypotheses and test procedures

A confirmative one-sided one-sample Poisson test will test whether the annualised total bleeding rate in patients with individual prophylaxis is at least 50% below the mean annualised total bleeding rate in the GENA-01 trial (i.e., if it is < 29).

Assumption

All BEs* and all months of prophylactic treatment will be pooled, each over all patients. The results will be denoted as y (number of BEs) and t (the pooled time frames in days). The total number of BEs y is assumed to be distributed with a Poisson distribution with parameter λ_{year}. Assuming a standard year of 365 days, y weighted by d/t (d = 365 days, t = sum over all observed days) will follow a Poisson distribution.

Tests on BE rates:

$$H_0: \lambda_{year} \geq 29 \text{ (1/2 of annualised mean bleeding rate in GENA-01)}$$

$$H_a: \lambda_{year} < 29,$$

where λ_{year} represents the annualised– rate of BEs per patient through the 6-month efficacy period, assuming a Poisson distribution for the frequency of BEs.

The annualised rate (λ_{year}) of BEs will be estimated along with its 2-sided (1-2α) x 100% confidence limits:

$$\lambda_{year} = d\frac{y}{t},$$

$$\lambda_{year,\,upper,1\text{-}2\alpha} = \frac{d}{t} x\ 0.5\ \chi^2_{(1-\alpha),2y+2}\ , \qquad \lambda_{year,\,lower,1\text{-}2\alpha} = \frac{d}{t} x\ 0.5\ \chi^2_{\alpha,2y}$$

with $\chi^2_{(1-\alpha),\nu}$

representing the upper 1-α percentile of the Chi-Square distribution with ν degrees of freedom, y the total sum of BEs documented during the observed prophylactic treatment period total, t the sum of all observed individual prophylactic treatment periods in days, and the constant d = 365 the assumed number of days per year.

H_0 is rejected if $\lambda_{year,\,upper,1\text{-}\alpha} < 29$. Type one error, one-sided : $\alpha \leq 0.0125$.

This confirmative test will be adjusted for a second test on the secondary efficacy variable 'annualised total bleeding rate in patients with 2x/week (or less) prophylaxis' with the Bonferroni rule. The maximum overall type-one error for both tests therefore will be 2 x α = 0.025.

There will be no adjustments for covariates in this primary analysis.

The individual annualised bleeding rate is estimated as follows:

$ATBR_{i,IP}$ = 365 x (number of all documented BEs in patients in the PROPH population between start of Prophylactic Treatment—Phase II and Study Completion Visit or withdrawal / (number of days between start of Prophylactic Treatment—Phase II and Study Completion Visit or withdrawal + 1)*

Notes: $ATBR_{i,IP}$ = annualised bleeding rate of patient i in study GENA-21b (individual prophylaxis scheme)

*The number of all documented BEs includes BEs treated with *Human-cl rhFVIII*, treated with other FVIII, and not treated during Prophylactic Treatment—Phase II.

a) Additional analysis

As an additional analysis of bleeding rates, the individual annualised bleeding rate will be analysed with a Poisson regression model and a Negative Binomial regression model, both including a correction for overdispersion. In these models, the number of BEs is the dependent variable and the log time of the observed prophylactic treatment period is used as an offset variable.

In addition, GENA-21b individualised annual bleeding rate data will be combined with GENA-01 individualised annual bleeding rate data in these models. The rate ratio comparing the individualised annual bleeding rates of the two trials and its corresponding 95% CI will be estimated from the model.

This will be done for spontaneous, traumatic, and all BEs.

In addition, the distribution of individual annualised total bleeding rates will be shown with descriptive statistics.

10.3.2 Secondary Objectives

***1. Comparison of annualised spontaneous bleeding rate of individualised tailored prophylaxis with the historical bleeding rate observed in patients having received on-demand treatment with* Human-cl rhFVIII**

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

This endpoint will be analysed in the same way as the primary endpoint (see Section 10.3.1), where the BEs are restricted to the spontaneous BEs. In case the upper limit of the 95% CI is below 19.25, the null hypothesis can be rejected.

No adjustment for multiple testing will be made.

In addition, descriptive analyses of individual bleeding rates (monthly, projected annually) will also be generated separately for the first 4 and the last 2 months (i.e., period starting with the 4-Month Visit) of Prophylactic Treatment—Phase II.

***2. Comparison of annualised total bleeding rate in patients with 2x/week (or less) prophylaxis with the historical bleeding rate observed in patients having received on-demand treatment with* Human-cl rhFVIII**

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

This endpoint will be analysed in the same way as the primary endpoint (see Section 10.3.1), where the patients are restricted to the subpopulation of patients with 2x/week (or less) prophylaxis in Prophylactic Treatment—Phase II.

The respective Poisson test will be adjusted for multiplicity with the Bonferroni rule as described for the primary endpoint.

3. Assessment of the median prophylactic dosing interval

Descriptive statistics will be provided on the distribution of the prophylactic dosing intervals overall and on the median prophylactic dosing interval per patient.

4. Assessment of the PK of* Human-cl rhFVIII *in terms of the FVIII coagulant activity (FVIII:C)

The initial PK will be used to determine an individual dosing scheme for Prophylactic Treatment—Phase II of the study.

The calculations for the PK will be made by applying one- or two- compartmental PK methods (as individually appropriate) to plasma levels obtained at predefined time points as described in Section 7.

The following PK parameters of *Human-cl rhFVIII* will be determined:

- In vivo half-life ($t_{1/2}$) (in case of two compartments both initial and terminal half-life)
- In vivo incremental recovery (IVR)
- Maximum plasma concentration (C_{max})
- Time for reaching maximum plasma concentration (T_{max})
- Mean residence time (MRT)

- Volume of distribution at steady state (Vss)
- Clearance (CL)

For these calculations, the *actual* potency of *Human-cl rhFVIII*, will be used.

The calculations will be made by applying compartmental PK methods based on plasma levels obtained at pre-defined time points. FVIII:C chromogenic and the one-stage assay results will be determined.

Descriptive statistics will be provided for all PK parameters for the treatment with *Human-cl rhFVIII*.

Calculation of dose/dosing-interval for individual prophylaxis scheme

Given the individual PK parameters and the respective one- or two-compartment model concentration time regression curve, it will be estimated for each patient for how long different doses are expected to provide FVIII:C plasma concentrations (one-stage assay) of ≥ 0.01 IU/mL.

The goal is to determine the maximum regular prophylactic dosing interval that can be achieved with a dose not exceeding 65 IU/kg and capable of maintaining a trough level of ≥ 0.01 IU/mL. Simulations will support the individual determination of the prophylactic interval and dose; the final decision on the prophylactic scheme will be taken by the investigator after consultation with the patient and Sponsor.

10.3.3 Additional Objectives

1. Assessment of the efficacy of* Human-cl rhFVIII *in the treatment of bleeding episodes (BEs)

Analyses will be performed on the BLEED and BLEED-PP populations. The efficacy will be evaluated by descriptive statistics on efficacy assessments per breakthrough bleeding, basic bleeding characteristics including severity, site, and type. The efficacy assessments will be presented in summary tables.

A BE is considered successfully treated if the efficacy is assessed as at least ‘good.’ The rate of successfully treated BEs (all BEs, spontaneous BEs, traumatic BEs) will be provided with a 95% exact confidence interval.

The frequency of BEs, the number of injections needed to treat a BE, the number of EDs, and study drug consumption data (FVIII IU/kg per injection, per BE, per month, per year) per patient and in total will be evaluated.

In an alternative analysis, the frequency of successfully treated BEs will be analysed with a generalised estimation equations (GEE) model accounting for the within-subject

correlation of bleeding assessments. The analysis populations will be the subjects with any BE in the BLEED population and the subjects with any BE in the BLEED-PP population.

2. Assessment of the efficacy of Human-cl rhFVIII in surgical prophylaxis

The following will be presented in frequency tables or with descriptive statistics:

- Efficacy evaluation by the surgeon and the haematologist (intra- and post-operatively and overall)
- Number of patients undergoing surgeries and number of surgeries (minor, major, total)
- Surgery characteristics (type and site, pre-planned (yes/no), reason, severity, expected and actual duration, expected and actual blood loss)
- Details on treatment with *Human-cl rhFVIII* (before, during, and after the surgical procedure (number of injections, dosing details, amount of IMP)
- Pre-, intra-, and post-operative FVIII plasma levels
- Any wound hematomas and whether they require surgical evacuation

3. Assessment of the correlation of VWF antigen concentration and half-life

Both Pearson's correlation coefficient and Spearman's rank correlation coefficient will be presented.

4. Assessment of the association between ABO type and half-life

The descriptive statistics of terminal half-lives will be presented by ABO type; if appropriate, the number and percentage of patients with each combination of ABO type and classified terminal half-life will be presented in a contingency table in addition.

5. Assessment of Human-cl rhFVIII consumption data (exploratory)

Descriptive statistics will be provided on FVIII consumption data (FVIII IU/kg per week/ month/year per patient).

10.3.4 Efficacy Analysis Plan for the "Sub-Study Extension Phase"

Efficacy will be evaluated by descriptive statistics.

- On bleeding rates (efficacy of prophylaxis)
- On efficacy assessments per treatment of 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).

10.3.5 Safety Analysis Plan

Adverse events

All AEs occurring after the initiation of study treatments (including events likely to be related to the underlying disease or a concomitant illness or medication as well as clinically significant abnormalities in laboratory parameters or vital signs) will be displayed in summary tables and listings.

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

- Any AE
- Any serious AE
- Any AE probably or possibly related to the IMP
- Any AE that begins within 24 hours after the end of an injection
- Any severe AE
- Any withdrawal due to AE
- Any AE by MedDRA Preferred Term (PT)
- Any AE by MedDRA System Organ Class (SOC)

Additionally, AEs will be summarised by severity and relationship to study treatment. These summary tables will feature total counts, prior exposure days to *Human-cl rhFVIII,* total amount of *Human-cl rhFVIII* used prior to the AE and the frequency of prophylactic treatment (up to 2x/week vs. 2x or more/week) 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), pulse, and body temperature will be presented by time point.

Routine laboratory data

Routine laboratory parameters will be listed for all patients, using indicators for values outside the associated reference ranges. Shift tables will be provided where appropriate.

Inhibitors against FVIII

All recorded determinations of inhibitors against FVIII will be listed. If any, the occurrence and cumulative incidence of inhibitors (inhibitor titre ≥ 0.6 and ≥ 5 BU, respectively) will be presented in total, and as percentage of the analysis population. If any, the changes between start and end of study will be summarised in a shift table.

10.3.6 Safety Analysis Plan for the "Sub-Study Extension Phase"

Except for vital signs which are not monitored in the "Sub-Study Extension Phase" all analyses will be performed as outlined in section 10.3.5

10.3.7 Handling of Missing Data

In general, missing data will not be imputed, and calculations pertaining to person-year computations will be based on observed values only.

Only in case of missing body weight will the last available weight measurement be used for calculating the dose per kg body weight or PK parameters (last observation carried forward).

10.4 Randomization, Stratification, and Code Release

Not applicable.

11 ETHICAL, REGULATORY, LEGAL, AND ADMINISTRATIVE ASPECTS

11.1 Ethical and Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. 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.

11.2 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 undergoes any 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.

11.3 Patient Information and Informed Consent

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

For patients not qualified to give legal consent, written consent must be obtained from the legal guardian (in the Netherlands, such patients are not allowed to participate in the study).

If patients from Japan wish to continue treatment with *Human-cl rhFVIII* in the "Sub-Study Extension Phase" after the completion visit in GENA-21b they have to freely give legal, written consent for participation in the "Sub-Study Extension Phase".

The investigator will explain that the patients are completely free to refuse to enter the study or the "Sub-Study Extension Phase", to withdraw from them at any time, without any consequences for their further care and without the need to justify. The investigator will complete the informed consent section of the eCRF for each patient enrolled.

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

11.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the co-ordinating investigator and the Sponsor before implementation. Any such amendments will be submitted to the IEC(s)/IRB(s) and/or competent authority as required by applicable regulations.

IEC/IRB approval will at a minimum be requested for any change to this protocol which could affect the safety of the patients or the objective or design of the study, which is associated with an increase in the dosage, duration of exposure to the IMP, or number of patients treated, results in the addition of a new test or procedure, or which drops a test intended to monitor safety.

11.5 Confidentiality of Patients Data

The investigator will ensure that the patient's confidentiality is preserved. On eCRFs 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 intended 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.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Periodic Monitoring

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

For this study, the first monitoring visit shall take place shortly after the inclusion of the first patient. Thereafter, 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 for the evaluation of the clinical study. Source data will be available for all data in the eCRFs, including all laboratory results.

12.2 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/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 the safety and efficacy of the IMP have been reported to the Sponsor.

13 REPORTING AND PUBLICATION

13.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines and the Sponsor's SOPs) was prepared by the Sponsor after completion of the GENA-21b study and will be prepared after completion of the "Sub-Study Extension Phase". The studies will be analysed separately and reported in 2 separate clinical study reports. The co-ordinating investigator will approve both final study reports after review.

13.2 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.

14 LIABILITIES AND INSURANCE

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

The investigator is responsible for dispensing the IMP according to this protocol as well as for the secure storage and safe handling of the IMP throughout the study.

15 REFERENCES

(1) Mannucci PM. Back to the future: a recent history of haemophilia treatment. Haemophilia. 2008 Jul;14 Suppl 3:10-8.

(2) Hironaka T, Furukawa K, Esmon PC, Fournel MA, Sawada S, Kato M, et al. Comparative study of the sugar chains of factor VIII purified from human plasma and from the culture media of recombinant baby hamster kidney cells. J Biol Chem. 1992 Apr 25;267(12):8012-20.

(3) Hokke CH, Bergwerff AA, Van Dedem GW, van OJ, Kamerling JP, Vliegenthart JF. Sialylated carbohydrate chains of recombinant human glycoproteins expressed in Chinese hamster ovary cells contain traces of N-glycolylneuraminic acid. FEBS Lett. 1990 Nov 26;275(1-2):9-14.

(4) Casademunt E, Martinelle K, Jernberg M, Winge S, Tiemeyer M, Biesert L, et al. The first recombinant human coagulation factor VIII of human origin: human cell line and manufacturing characteristics. Eur J Haematol. 2012 Aug;89(2):165-76.

(5) Sandberg H, Kannicht C, Stenlund P, Dadaian M, Oswaldsson U, Cordula C, et al. Functional characteristics of the novel, human-derived recombinant FVIII protein product, human-cl rhFVIII. Thromb Res. 2012 Nov;130(5):808-17.

(6) Kannicht C, Ramstrom M, Kohla G, Tiemeyer M, Casademunt E, Walter O, et al. Characterisation of the post-translational modifications of a novel, human cell line-derived recombinant human factor VIII. Thromb Res. 2013 Jan;131(1):78-88.

(7) National Hemophilia Foundation. MASAC Recommendation #179 [www.hemophilia.org] 2013.

(8) Makris M. Prophylaxis in haemophilia should be life-long. Blood Transfus. 2012;10:165-8.

(9) Collins PW, Bjorkman S, Fischer K, Blanchette V, Oh M, Schroth P, et al. Factor VIII requirement to maintain a target plasma level in the prophylactic treatment of severe hemophilia A: influences of variance in pharmacokinetics and treatment regimens. J Thromb Haemost. 2010 Feb;8(2):269-75.

(10) Collins PW, Fischer K, Morfini M, Blanchette VS, Bjorkman S. Implications of coagulation factor VIII and IX pharmacokinetics in the prophylactic treatment of haemophilia. Haemophilia. 2011 Jan;17(1):2-10.

(11) Coppola A, Franchini M. Target of prophylaxis in severe haemophilia: more than factor levels. Blood Transfus. 2012 Dec 21;1-3.

(12) Ljung R, Auerswald G, Benson G, Jetter A, Jimenez-Yuste V, Lambert T, et al. Novel coagulation factor concentrates: Issues relating to their clinical implementation and pharmacokinetic assessment for optimal prophylaxis in haemophilia patients. Haemophilia. 2013 Feb 6;

(13) Viuff D, Barrowcliffe T, Saugstrup T, Ezban M, Lillicrap D. International comparative field study of N8 evaluating factor VIII assay performance. Haemophilia. 2011 Jul;17(4):695-702.

(14) HJHS 2.1: http://www.wfh.org/en/page.aspx?pid=885