octapharma

CLINICAL STUDY REPORT

GENA-21b

16.1.9 Documentation of Statistical Methods

STATISTICALANALYSIS PLAN
GENA-21b

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

Development Phase lllb

Version Final 5.0

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(according to Protocol Version 5, 26 October, 20 l 5 and
according to Protocol Version 9, 7 June, 2017 (Japanese extension study),
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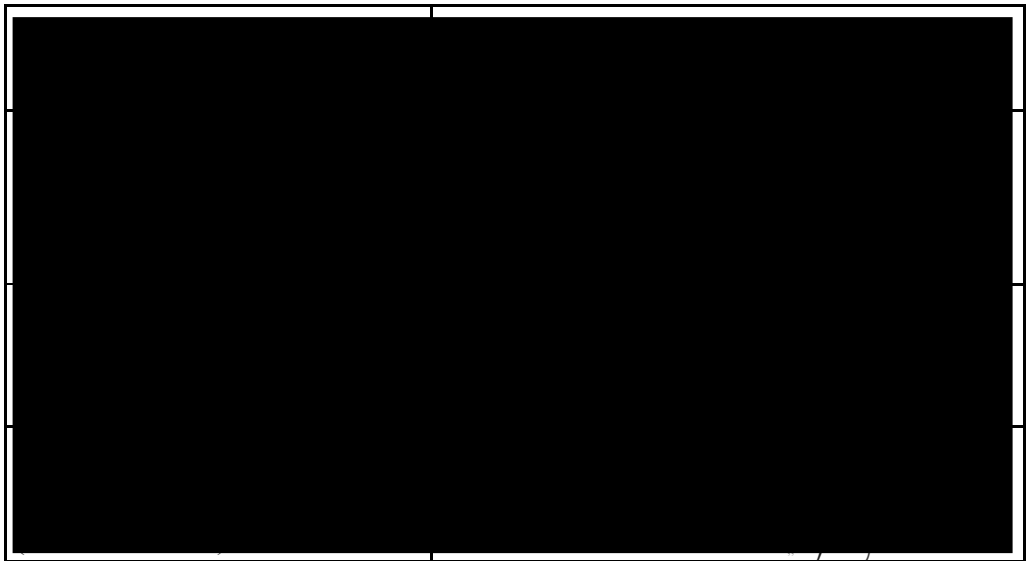

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ABBREVIATIONS AND DEFINITIONS

ABO	Blood type system
ABR	annualized bleeding rate
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$ASBR_{i,IP}$	individual annualized spontaneous bleeding rate of patient i in study GENA-21b (individual prophylaxis scheme)
$ATBR_{i,IP}$	individual annualized traumatic bleeding rate of patient i in study GENA-21b (individual prophylaxis scheme)
$ATrBR_{i,IP}$	individual annualized bleeding rate of patient i in study GENA-21b (individual prophylaxis scheme)
AUC	area under the curve (from baseline to infinity)
BE	bleeding episode
BILI	total bilirubin
BLEED	Population of bleedings treated with Human-cl rhFVIII
BLEED-PP	Population of bleedings treated with Human-cl rhFVIII – per protocol
Bleeding rates	- Annualized total bleeding rate: Frequency of any bleeding over all patients divided by the sum of observation time period over all patients standardized to one year (ATBR) - Annualized spontaneous bleeding rate: like ATBR only with spontaneous bleedings (ASBR) - Annualized traumatic bleeding rate: like ATBR only with traumatic bleedings (ASBR) - Individual annualized bleeding rate: Frequency of bleedings per patient divided by the individual observation time period standardized to one year.
BMI	Body mass index
BU	Bethesda Unit
BW	body weight
C_0	Plasma concentration directly after infusion according to PK model
CI	confidence interval
CL	clearance
C_{max}	maximum plasma concentration
CREA	serum creatinine
CSR	Clinical study report
ED	exposure day
FVIII	factor VIII
FVIII:C	FVIII coagulant activity
GCP	Good Clinical Practice
GEE	Generalized Estimation Equation
HCT	hematocrit
HGB	hemoglobin

HIV	human immunodeficiency virus
HJHS	Hemophilia Joint Health Score
IMP	investigational medical product
ITT	Intent to Treat analysis population: All patients in the safety analysis population for whom any data was collected after treatment with Human-cl rhFVIII.
IU	International Unit
IVR	in-vivo recovery
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRT	mean residence time
PK	pharmacokinetic
PK (Population)	All patients in the ITT population who started the initial PK assessment with Human-cl rhFVIII.
PK-PP	PK population, per protocol
PLAT	platelet count
PP	per protocol
PROPH	Population of patients on individual prophylactic treatment schedule (Prophylactic Treatment—Phase II)
PROPH-PP	Population of patients on individual prophylactic treatment schedule (Prophylactic Treatment—Phase II) – per protocol
PT	Preferred term
PTPs	previously treated patients
RBC	red blood cell count
rhFVIII	Recombinant human factorVIII
SAE	serious adverse event
SAF	Safety Population
Safety-INF	infusions with Human-cl rhFVIII to patients of the Safety population.
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
SURG	Surgical interventions with bleeding prevention with Human-cl rhFVIII
SURG-PP	Surgical interventions with bleeding prevention with Human-cl rhFVIII - per protocol
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum plasma concentration
ULN	upper limit of normal range
V_1=V	volume of distribution in central compartment
Vss	volume of distribution at steady state
vWFAg	von Willebrand factor antigen
WBC	white blood cell count
WHO DRL	World Health Organization Drug Reference List

1 PURPOSE

This Statistical Analysis Plan describes all statistical analyses to be performed on data collected in study GENA-21b in full detail, and the resulting output that will be compiled for two integrated clinical study reports: for the main study and for the Japanese extension study.

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

Each integrated clinical study report (CSR) will closely follow the ICH guideline for industry on topic E3 (Structure and Content of Clinical Study Reports), and include the following appendices covered in this SAP:

The CSRs will include

Tables, figures and listings included in or referred to but not included in the text of the CSRs (section 14 of the CSRs)

- Demographic Data Summary figures and tables
- Efficacy Data Summary figures and tables
- Safety Data Summary figures and tables

Listings provided as appendices to the CSRs

- Patient Data Listings (section 16.2 of the CSRs)

2 INTRODUCTION

Human-cl rhFVIII is a fourth-generation recombinant human factor VIII (rhFVIII) concentrate 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.

This is a prospective, non-controlled, open label, multinational, multicenter 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 patients ≥ 18 years of age will be enrolled to with the aim to have evaluable data on 50 patients. Patients will be recruited from about 30 haemophilia treatment centers worldwide. Approximately 10 patients will be enrolled from Japan. The study consists of three (3) phases, i.e., the PK Evaluation Phase, the Prophylactic Treatment –Phase I, and the Prophylactic Treatment –Phase II. The study duration for each patient will be approximately 7 to 9 months, and the overall study duration will be about 3 years.

"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.

Administration of treatment

A single intravenous (iv) infusion of *Human-cl rhFVIII* (60 ± 5 IU/kg BW) will be used for the determination of full pharmacokinetics including Incremental Recovery.

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

In Prophylactic Treatment Phase II, the PK-tailored dose and dosing interval will be determined individually for each patient. Based on an appropriate PK model, various dosing intervals (usually 12-hour intervals) and corresponding doses (in IU/kg) will be calculated, which hypothetically lead to FVIII:C plasma concentrations of at least 0.01 IU/mL at the end of the respective injection interval.

The goal is to use the maximum regular prophylactic dosing interval that can be achieved with a maximum dose of preferably not more than 65 IU/kg (Wording in Japanese protocol version 09: "the maximum dose should not exceed 65 IU/kg") and that maintains a trough level of ≥ 0.01 IU/mL.

The dosing recommendation may also change in certain situations (see protocol chapter 6.4.3 for additional information).

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

"Sub-Study Extension Phase" to GENA-21b (Japan):
Patients will continue to be treated prophylactically after the completion of 6 months in Prophylactic 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. 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 main study.

3 STUDY OBJECTIVES

3.1 Primary Objective

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

3.2 Secondary Objectives

- To compare the **annualized spontaneous bleeding rate** of individually tailored prophylaxis with the historical bleeding rate observed in patients having received on-demand treatment with *Human-cl rhFVIII*
- To compare the **annualized 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*
- To assess the **median prophylactic dosing interval**
- To assess the **PK of *Human-cl rhFVIII*** in terms of FVIII:C
- To assess the **safety of *Human-cl rhFVIII***

3.3 Additional objectives

- To assess the efficacy of *Human-cl rhFVIII* in the **treatment of breakthrough bleeding episodes (BEs)**
- To assess the efficacy of *Human-cl rhFVIII* in **surgical prophylaxis**
- To assess the correlation of **vWF antigen** concentration and half-life of *Human-cl rhFVIII*
- **To assess the association between ABO blood type and half-life of *Human-cl rhFVIII***
- To assess ***Human-cl rhFVIII* consumption data**

3.4 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**

3.5 Assessment of Study Objectives

3.5.1 Annualized total bleeding rate (ABR)

3.5.1.1 Main study

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

1st secondary endpoint: Reduction of the annualized spontaneous bleeding rate observed in the GENA-01 study (38.5 spontaneous bleeding episodes per patient per year) by 50% during individually tailored prophylaxis

2nd secondary endpoint: Reduction of the annualized bleeding rate observed in GENA-01 by 50% in patients with 2x/week prophylaxis or less

The frequency of all / only spontaneous BEs* under prophylactic treatment will be calculated.
The time period for Prophylactic Treatment Phase II will comprise:

- Each patient's time between first prophylactic treatment with Human-cl rhFVIII in Prophylactic Treatment Phase II until last prophylactic treatment + actual individual dosing interval or study completion, whichever comes first, minus time periods from start of a surgery until restart of regular prophylactic treatment
- The number of BEs counted for Prophylactic Treatment Phase II efficacy assessment will comprise:
  All* / only spontaneous BEs starting during the time periods for Prophylactic Treatment Phase II defined above.

*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. BEs categorized as post-operative will not be included in the primary prophylactic treatment assessment.

For the primary analysis of the primary objective and the two secondary objectives all BEs and all months of Prophylactic Treatment Phase II will be pooled, each over all patients and an overall rate of BEs per year (annualized bleeding rate) will be calculated from this.

In addition the individual annualized bleeding rate will be calculated per patient.

The annualized bleeding rate in the historical comparison study GENA-01 will be determined in the following way from the GENA-01 data:

- Each patient's time between the patient's 96h visit after the 2nd PK of the cross-over part of the study and the completion visit. Other than for the estimation of the annualized bleeding rate in the GENA-21b study time periods after prophylaxis for surgeries will not be subtracted from the on demand time period in the GENA-01 trial, as there would be no clear definition of the time periods to be excluded which are comparable to the time periods excluded from the GENA-21b trial. However, not excluding these time periods from the calculation for the GENA-01 trial will only have very minor impact (only two surgeries, one of them of minor severity) and the impact will be conservative, i.e. slightly underestimate the GENA-01 ABR as there were no BEs associated with the surgical interventions

- The number of BEs counted will comprise: All / only spontaneous BEs starting during the on demand treatment period defined above.

The on demand treatment periods and the BEs will be pooled over all patients in the GENA-01 study like the prophylactic treatment periods and the BEs in the GENA-21b study.

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

Endpoint: "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"

An overall annualized bleeding rate according to the primary endpoint in the main study will be calculated taking the sum of all BEs over all patients during the extension period and the sum of all observation periods over all patients during the extension phase into account.

In addition the individual annualized bleeding rate will be calculated per patient.

3.5.2 Prophylactic dosing interval (only main study)

3rd secondary endpoint: Median prophylactic dosing interval during individually tailored prophylaxis

The median time between two prophylactic doses of Human-cl rhFVIII in the Prophylactic Treatment Phase II will be determined per patient. The time between the last prophylactic treatment before a surgery treated with Human-cl rhFVIII and the restart of routine prophylactic treatment will be excluded from this analysis. Regarding breakthrough BEs only subsequent prophylactic treatments will be taken into account for this analysis, i.e. if after a prophylactic administration the next administration is due to bleeding, the next interval to be counted will be calculated from the next two successive prophylactic treatments.

3.5.3 Determination of FVIII:C and PK of Human-cl rhFVIII (only main study)

FVIII:C will be determined by two independent and commonly used laboratory assay techniques:

- The One-stage (OS) assay and the
- Chromogenic (CHR) assay.

Pharmacokinetic calculations will be done on data from both assays in the final analysis. However, only the one-stage assay will be used for the determinations of the treatment schedule for Prophylactic Treatment—Phase II.

3.5.3.1 Actual and Labelled Potencies

For all batches of *Human-cl rhFVIII* the actual potencies, i.e. the content of FVIII expressed as IU/vial, are provided by a central laboratory. The actual potencies will be determined using both assay methods, CHR and OS, and used accordingly for calculations based on each assay. These data will be provided to the statistician and at least the one-stage assay result for the potencies will be available at time of the individual PK analyses for the determinations of the treatment schedule for Prophylactic Treatment—Phase II. If the central laboratory will not provide one single potency determination per lot per assay, the potency for one lot with one assay will be calculated as the geometric mean of the values provided for the lot/ assay method.

Calculation of pharmacokinetic parameters will be based on the actual potency whereas dosing will be based on the labelled potency.

3.5.3.2 Pharmacokinetic Parameters

Full pharmacokinetic assessments will be made after administration of 60 ± 5 IU/kg (labelled potency) based on blood sampling before infusion and 0.5 h, 1 h, 3 h, 6 h, 9 h, 24 h, 30 h, 48 h, and 72 h after the end of infusion. The actual sampling time points will be documented.

Pharmacokinetic assessments will be started only if the patient is not actively bleeding and has respected a washout phase of at least 96 hours, if possible (Additional remark in Japanese protocol: "A washout period of at least 72 hours would be acceptable only if a patient is at a high risk of bleeding.").

The following pharmacokinetic parameters of *Human-cl rhFVIII* will be determined by applying one- or two- compartmental PK methods (as individually appropriate):

- 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 (V_{ss})
- Clearance (CL)

For these calculations, the *actual* potency of *Human-cl rhFVIII*, will be used; for formulas see Chapter 10. PK results for both the chromogenic and the one-stage assay results will be determined.

3.5.3.3 Calculation of dose/dosing-interval for individual prophylaxis scheme

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

a) Planned dose / dose interval calculation

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

b) The goal is to determine the maximum regular prophylactic dosing interval that can be achieved with a maximum dose of not more than 65 IU/kg maintaining a trough level of

≥ 0.01 IU/mL and avoiding estimated C_0 > 2 IU/mL. The simulations will support the individual determination of the prophylactic interval and dose.

Considerations for dose recommendations for start of phase II by Octapharma

- 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 will be taken by the investigator after consultation with the patient and the 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). If, after a dose increase, patients still experience unacceptable bleeding episodes, the dosing interval should be shortened.

3.5.4 Clinical Safety

3.5.4.1 Main study

4th secondary endpoint: Safety and tolerability of Human-cl rhFVIII by monitoring adverse events (AEs) throughout the study

Clinical safety and tolerability will be assessed by monitoring of adverse events, and additionally by vital signs (only during initial PK) and laboratory parameters including inhibitors against FVIII:

- Adverse Events will be monitored throughout the whole study period and the following data will be collected:
    - Reported term
    - Date/time of onset
    - Severity (mild, moderate or severe)
    - Seriousness (non-serious or serious) including individual seriousness criteria
    - Causality (probable, possible, unlikely, not related, unclassified)
    - Outcome (recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal, unknown)
    - Date of outcome

  - Actions taken in general (none, medication or other therapy started, test performed, other) and IMP-related actions (none, product withdrawn, dose reduced, dose increased)
- The safety lab panel (only at screening and at certain time points in case of surgery, see 3.5.6) consists of the following measurements:
  - Haematology: red blood cell count (RBC), white blood cell count (WBC), haemoglobin (HGB), haematocrit (HCT), and platelet count (PLAT).
  - Clinical chemistry: total bilirubin, alanine amino transferase (ALT), aspartate transaminase (AST), urea, serum creatinine (CREAT), lactate dehydrogenase (LDH)
- Vital signs (blood pressure, pulse, body temperature) will be assessed at the following time-points:
  - at screening (all patients)
  - at initial PK visit (may be identical to screening visit) before injection as well as 1 and 72 hours after the end of injection

  and at certain time points in case of surgery, see 3.5.6.

- Immunogenicity

Inhibitor activity (using the Nijmegen modification of the Bethesda assay) will be determined. This will be done at the following occasions:

- at initial PK visit, before infusion
- Prophylactic Treatment Phase I: Day 14 visit (14-21 days after administration of first dose of Human-cl rhFVIII on PK visit Day 1
- Prophylactic Treatment Phase I: Day 30 visit (30 days ± 3 days after administration of first doe of Human-cl rhFVIII on PK visit Day 1); only , if not visit does not coincide with End-of-phase I visit
- Prophylactic Treatment Phase II: End-of-phase I visit
- Prophylactic Treatment Phase II: 2-month visit
- Prophylactic Treatment Phase II: 4-month visit
- at the completion visit (6 months after start of Prophylactic Treatment—Phase II)
- 3-8 weeks after the end of a surgery (may coincide with any other study visit where inhibitor testing is scheduled)

In case inhibitor development is suspected, additional FVIII inhibitor tests will be performed (preferably within 15 days of becoming aware of a positive result) and documented.

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

Endpoint: "Safety of Human-cl rhFVIII by monitoring adverse events (AEs) and inhibitors against FVIII throughout the "Sub-Study Extension Phase""

Clinical safety and tolerability will be assessed by monitoring of adverse events and of inhibitors against FVIII:

- Adverse Events will be monitored throughout the whole study period. The data collected corresponds to the respective data in the main study.
- Immunogenicity

Inhibitor activity (using the Nijmegen modification of the Bethesda assay) will be determined. This will be done at the following occasions:

- Completion visit GENA-21b (main)/ Screening Visit "Sub-Study Extension Phase"
- 6-monthly follow-up visits (+/- 2 weeks)
- Completion visit of "Sub-Study Extension Phase"

3.5.5 Efficacy of on-demand treatment of breakthrough bleeding episodes

3.5.5.1 Main study

1st additional endpoint: Descriptive efficacy of Human-cl rhFVIII in the treatment of breakthrough BEs

For all bleeding episodes[a] occurring during the study period (i.e. starting with the first treatment day with *Human-cl rhFVIII* after the PK (Prophylactic Treatment - Phase I) until the completion visit (6-month visit) after Prophylactic Treatment - Phase II the following data will be collected:

- Type of BE (spontaneous, traumatic, post-operative, other)
- Site(s) of BE
- Start date and time of occurrence/of noticing the BE
- Severity of the BE (minor, moderate, major, life threatening)
- Date and time of end of BE
- Details of dose(s) and batch number used to treat BE (in IU).
- Dates and times of study product infusions.
- Details on any concomitant medication used
- For those BEs treated with *Human-cl rhFVIII* there will be the following efficacy assessment at the end of the BE (by patient, together with the Investigator in case of on-site treatment):

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

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

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

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

[a].If the treatment of a BE at one site is interrupted for > 48 hours, the events are to be recorded as two separate BEs; if another than the original bleeding site is affected, the events are to be recorded as separate BEs at any time. If there are several simultaneous bleeding sites, each bleeding site is recorded as a separate BE

The assessment will be made at the end of a BE. A BE will be defined as "*successfully treated*" if the efficacy rating is assessed as either 'excellent' or 'good'.

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

Endpoint: "Descriptive efficacy of Human-cl rhFVIII in the treatment of breakthrough BEs"

For all bleeding episodes occurring during the study period (i.e. starting with the completion visit GENA-21b/Screening visit "Sub-study Extension Phase" until the completion visit of the "Sub-study Extension Phase") the same data as during the main study (see above) will be collected.

All BEs treated with *Human-cl rhFVIII* will be assessed regarding the efficacy in the same way and on the same scale as in the main study (see above).

3.5.6 Surgical Prophylaxis

2nd additional endpoint: Descriptive efficacy of Human-cl rhFVIII in surgical prophylaxis

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

- BW within 12 hours before start of the surgery (kg).
- Type of surgery (planned or emergency)
- Location of surgery.
- Severity of surgery (minor, major), see details in chapter 3.5.6.1.
- Expected duration of surgery.
- Actual duration of surgical procedure (start and end times, i.e., skin to skin).
- Details on dose(s) of Human-cl rhFVIII given pre-, intra-, or postoperatively; see details in chapter 3.5.6.2.
- Pre-(within 3h before start of the surgery), intra-, and postoperative FVIII plasma levels; see details in chapter 3.5.6.3.
- Expected and actual blood loss; see details in chapter 3.5.6.4.
- 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 details in chapter 3.5.6.5.
- Details on concomitantly administered products, including any blood or blood product transfusions but excluding drugs given for routine anaesthesia.
- Monitoring of AEs.

3.5.6.1 Classification of Surgeries

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

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

The classification will be made prospectively. All other surgeries are classified as minor.

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

- A pre-operative administration is defined as any dose of *Human-cl rhFVIII* applied within 3 hours prior to surgery start.
- An intra-operative administration is defined as any infusion of *Human-cl rhFVIII* applied during surgery.
- A post-operative administration is defined as any dose of *Human-cl rhFVIII* applied after the end of the surgery ("end of surgery" is defined as "last suture") to the time the patient returns to his regular prophylactic FVIII treatment regimen.

3.5.6.3 Time Points for FVIII Plasma Level Documentation

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

- Immediately (≤30 minutes) before and after pre-operative infusion of study drug.
- Immediately (≤30 minutes) before and after each intra-operative bolus dose (if any).
- Immediately (≤30 minutes) before and after each post-operative dose (if any); in case of major surgery: mandatory for the first 3 post-operative doses.

3.5.6.4 Estimation of Blood-Loss

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

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

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

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

3.5.6.5 Efficacy Assessment 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:

Assessment at the end of the surgery (= after last suture) by surgeon:

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

Post-operatively by haematologist:

- Excellent: No postoperative bleeding or oozing that is not due to complications of surgery. All postoperative bleeding (due to complications of surgery) is controlled with *Human-cl rhFVIII*, as anticipated for the type of procedure.
- Good: No postoperative bleeding or oozing that is not due to complications of surgery. Control of postoperative bleeding due to complications of surgery required increased dosing with *Human-cl rhFVIII* or additional infusions, not originally anticipated for the type of procedure.
- Moderate: Some postoperative bleeding and oozing that is not due to complications of surgery; control of postoperative bleeding required increased dosing with *Human-cl rhFVIII* or additional infusions, 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 concentrate.

In addition 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 without predefined assessment criteria at the end of the postoperative period.

Based on this overall efficacy assessment, a surgery will be defined as **successfully** treated if this assessment was either 'excellent' or 'good'.

Remark: BEs and treatments documented in the surgery part of the CRF will solely be analysed in relation to the efficacy of *Human-cl rhFVIII* as haemostatic medication used in surgical interventions; these data will not be considered in the statistical analyses related to the efficacy of *Human-cl rhFVIII* in the treatment of BE to avoid double reporting and to take into account the very different circumstances under which these data have been collected.

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

Endpoint: Descriptive efficacy of Human-cl rhFVIII in surgical prophylaxis

For any surgical procedure performed during the study, the same data will be recorded as in the main study (see above).

The classification of surgeries, definitions of pre-, intra-, and post-operative doses, time points for FVIII plasma level documentation, estimation of blood-loss, and the efficacy assessment of surgical prophylaxis will be the same as in the main study.

3.5.7 vWF antigen (vWFAg) (only main study)

3rd additional endpoint: Correlation between vWF antigen concentration and the half-life of Human-cl rhFVIII

- vWFAg will be assessed at the following time-point:
    - at initial PK visit: before infusion

3.5.8 Half-life association with ABO blood type (only main study)

4th additional endpoint: Association between ABO blood type and half-life of Human-cl rhFVIII

- The association between the ABO blood type and the *half-life of Human-cl rhFVIII* will be assessed per assay

3.5.9 Human-cl rhFVIII consumption data (only main study)

5th additional endpoint: Human-cl rhFVIII consumption data (FVIII IU/kg per month per patient) during individually tailored prophylaxis

Study drug consumption data (FVIII IU/kg, extrapolated to monthly and yearly usage) per patient will be evaluated for prophylactic treatment in Prophylactic Treatment—Phase II, for treatment of BEs during Prophylactic Treatment—Phase II, and over both.

Study drug consumption data will be analyzed in the same way for Prophylactic Treatment Phase I.

The time period for Prophylactic Treatment Phase I will comprise:

- Each patient's time between 72 h PK visit until last prophylactic treatment before End of Phase I visit + actual individual dosing interval or day before End of Phase I visit whichever comes first minus time periods from start of a surgery until restart of regular prophylactic treatment

4 STUDY DESIGN

4.1 General Design and Plan

This is a prospective, open-label, multicenter 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. There is no prospective control group.

4.1.1 Main study

The primary objective of this clinical study is to compare the annualized total bleeding rate of individually tailored prophylaxis with the historical bleeding rate observed in patients having received on-demand treatment with *Human-cl rhFVIII* from study GENA-01. Secondary objectives are to compare both the annualized spontaneous bleeding rate and the annualized total bleeding rate in patients with 2x/week (or less) prophylaxis of individually tailored prophylaxis with the historical bleeding rate observed in patients having received on-demand treatment with *Human-cl rhFVIII*. Further secondary objectives are to assess the prophylactic dosing interval, FVIII consumption data, the PK of *Human-cl rhFVIII* and the safety of *Human-cl rhFVIII*. Additional objectives are the efficacy of *Human-cl rhFVIII* in the treatment of breakthrough BEs and in surgical prophylaxis.

Data will be collected on at least 50 previously treated male patients ≥ 18 years of age recruited from about 30 haemophilia treatment centres worldwide. Up to 55 patients may be enrolled to compensate for potential drop-outs.

The study consists of three phases, i.e., the PK Evaluation Phase, the Prophylactic Treatment-Phase I, and the Prophylactic Treatment-Phase-II.

- The PK Evaluation Phase will last for 3 days.
- In Prophylactic Treatment-Phase I 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 and the dose and dosing interval for the Prophylactic Treatment—Phase II has been determined.
- In Prophylactic Treatment-Phase II (individually tailored treatment schedule), patients will be treated prophylactically for 6 months starting with the treatment schedule as recommended based on the analysis of individual PK data obtained at the Initial PK Visit.

The study duration for each patient will be approximately 7 to 9 months, and the overall study duration will be about 3 years. The end of the study is defined as the last visit of the last patient participating in the study. The study will be stopped prematurely if more than 3 patients develop a neutralizing antibody (inhibitor) to *Human-cl rhFVIII*.

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

After completing the GENA-21b study 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 2019.

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.

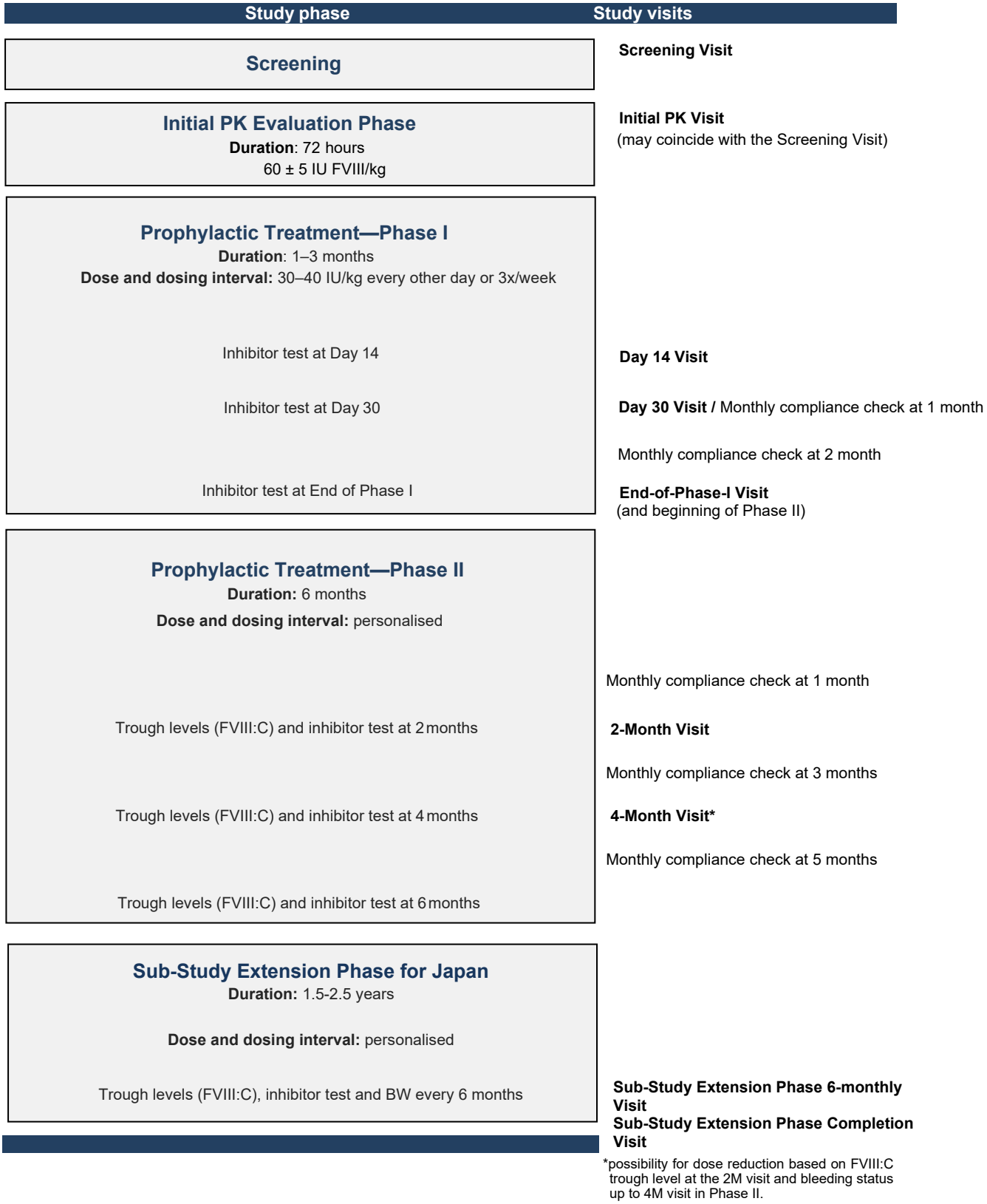
Patients are eligible to participate in the "Sub-Study Extension Phase" if they completed the GENA-21b study with 6 months of prophylactic treatment in Treatment-Phase II and voluntarily gave fully informed written and signed consent before any Sub-Study related procedures are conducted. The completion 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*.

The main study and the "Sub-Study Extension Phase" will end up in two different analyses, two different reports and usually will only share the same demographic data. In addition, wherever possible and necessary baseline values for the "Sub-Study Extension Phase" should be taken from the completion visit of the main study, if there was no respective examination at screening for the "Sub-Study Extension Phase".

Figure 1 provides a study overview:

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



4.2 Sample Size

4.2.1 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 (50% of the annualized bleeding rate in the GENA-01 trial [2]) (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 annualized bleeding rate equals the estimated mean annual bleeding rate in the GENA-08 trial [4]

Scenario 2 assumes that the annualized bleeding rate equals the upper 2-sided 95% CI of study GENA-09 (i.e., 12*0.554) [5]

Scenario 3 assumes that the annualized bleeding rate equals 2 times the upper 2-sided 95% CI of study GENA-09

4.2.2 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 $\lambda_{\text{half year},0} = n \times 6 \times 29$ (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.

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

For the "Sub-Study Extension Phase", no inferential analysis including formal hypothesis testing was 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.

4.3 Randomization and Blinding

Not applicable.

4.4 Study Assessments

For assessments directly related to the evaluation of the primary, secondary and additional endpoints please refer to section 9 and section 10. For assessments directly related to the evaluation of safety refer to section 11.

The following parameters will be assessed to allow a meaningful characterisation of the study population and to collect background information required for medical evaluation of study events:

- Patient demographics and baseline characteristics: ethnicity, age, gender, height, weight, body mass index (BMI), ABO blood typing, target joints
- Medical History including FVIII inhibitor history, HIV status, and bleeding frequency in the previous 6 months
- Previous treatment with FVIII concentrates
- Concomitant Medication will be recorded throughout the trial and throughout the "Sub-study extension phase"
- Physical examinations will be performed at screening and at the end of the 6-month visit. For patients in the sub-study physical examination will be performed in addition
  - on the Screening visit "Sub-study extension phase", if day not identical with completion visit of main study, and
  - on the completion visit of the "Sub-study Extension Phase".
- Haemophilia joint health score will be recorded at screening (HJHS evaluation done in the 3 months prior to screening is acceptable) ([2] see APPENDIX I: HAEMOPHILIA JOINT HEALTH SCORE – SUMMARY SCORE SHEET, VERSION 2.1) (only main study).

5 STUDY POPULATIONS

5.1 Subject Disposition

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

5.1.1 Main study (does not refer to Japanese extension phase of the study)

- Safety Population (SAF): 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*.
- 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 protocol Section 5.3.2) or several *unexplained* and significant deviations from the recommended dose regimen and/or dosing frequency.
- PK analysis population (PK): All patients in the ITT population who started the initial PK assessment with *Human-cl rhFVIII*.
- PK per protocol (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 criterion:
    - 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 ≥ 0.05 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 population:
  - (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 PROPH population, which are not in subpopulation (1))
  - For patients who change treatment frequency during Prophylactic Treatment—Phase II from 2x/week or less to more than 2x/week or vice versa data (bleeding rates, etc,) will be counted only up to the (first) change.
- Population of patients with observation time both in Prophylactic Treatment Phase I and Phase II (PROPHc): All patients in the PROPH population with an observation time of at least 1 month (30 days) in both Prophylactic Treatment Phase I and II.
  Observation times in
  Prophylactic Treatment Phase I: 72h visit after end of PK until day before End-of-phase I visit
  Prophylactic Treatment Phase II: Day of End-of-phase I visit until last prophylactic dose + actual dosing interval or day of completion visit, whatever comes first
- PP population of patients with observation time both in Prophylactic Treatment Phase I and Phase II (PROPHc-PP): All patients in the PROPHc population of the study
  - who are members of the PROPH-PP population
  - with at least 6 weeks (42 days) of standard prophylactic treatment (Prophylactic Treatment—Phase I) with *Human-cl rhFVIII*
  - who have no significant dosing or treatment errors during Prophylactic Treatment Phase I, e.g., several unexplained interruptions of standard prophylaxis with *Human-cl rhFVIII*, e.g. >20% of prophylactic injections were not given within the prescribed treatment intervals (± 1 day)
- 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 concentrate was documented.
- Surgery population (SURG): All documented surgical interventions of patients in the ITT population for which
  - any amount of *Human-cl rhFVIII* prior to, during or after the surgery is documented and
  - no other FVIII concentrate is documented within 24 hours prior to surgery[a].
- Surgery per-protocol population (SURG-PP): All documented surgical interventions in the SURG population of patients in the PP population for which
  - any amount of *Human-cl rhFVIII* prior to, during or after the surgery is documented and
  - no other FVIII concentrate is documented within 72 hours prior to, during or after the surgery.
- Infusions analysis population (Safety-INF): All documented infusions with *Human-cl rhFVIII* to patients of the Safety population.
  AEs will be related to a patient's infusion No. i if the AE starts during infusion No. i or within 24 hours after infusion No. i but starts before the same patient's infusion No. i+1

- Subpopulations Japanese/Non-Japanese (J/NJ)
  - Japanese patients: All patients in the ITT population from Japanese centers with race="Asian" .
  - Non-Japanese: All other patients.
  Remark: The Japanese authorities require analyses for Japanese patients versus all patients. Usually the analysis for the Japanese subgroup will show 1) the results for the Japanese subgroup, 2) the results for the non-Japanese patients and 3) the results for all patients; so the requested comparison is included.

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; the SURG population is considered primary for analysis of efficacy data on surgeries. The PROPHc population is the primary study population for the within-subject comparisons of bleeding rates between Prophylactic Treatment Phases.

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

[a] For the analyses of surgeries only surgeries performed under *Human-cl rhFVIII* will be considered; clearly the assessment of the efficacy of *Human-cl rhFVIII* in surgeries should not be biased by inclusion of data from surgeries where other FVIII concentrates were used prior to the surgery. The surgeries in subjects of the ITT analysis population who are eligible for analysis in this sense will be referred to as 'Surgery Population'.

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.

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

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

- **Safety Analysis Population (SAF-EXT):**
  All patients enrolled into the "Sub-Study Extension Phase" who received at least one dose of *Human-cl rhFVIII* during this phase
- **Intent to Treat (ITT-EXT) analysis population:**
  All subjects in the SAF-EXT population for whom any data was collected post treatment with Human-cl rhFVIII;
- **Per Protocol (PP-EXT) analysis population:**
  All subjects in the ITT-EXT 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 were excluded from the PP population of the main study because they violated one or more in/exclusion criteria
  - Subjects who fulfill the following exclusion criteria of the extension study:
    - 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-EXT):**
  All subjects in the ITT-EXT population who have at least one prophylactic treatment in the extension study.
- **Per-protocol population of subjects on prophylactic treatment schedules (PROPH-PP-EXT):**
  All subjects in the PP-EXT 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-EXT):**
  All documented bleeds during the extension phase - except those occurring during and after surgery - of subjects in the ITT-EXT population for whom
  - any amount of treatment with *Human-cl rhFVIII* is documented and which
  - start between first BE treated with *Human-cl rhFVIII* in the extension study and the completion visit of the extension study.
- **Population of bleedings per protocol (BLEED-PP-EXT):**
  All documented bleeds in the BLEED-EXT population of subjects in the PP-EXT population.
- **Surgery population (SURG-EXT):**
  All documented surgical interventions during the extension phase of subjects in the ITT-EXT population for whom
  - 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-EXT):**
  All documented surgical interventions during the extension phase of subjects in the PP-EXT population for whom
  - 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-EXT 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.

5.2 Major Protocol Deviations

Major protocol deviations will be assessed and listed as part of the database lock procedures prior to data analysis, and will include:

- Violation of inclusion or exclusion criteria*EXT
- Concomitant medication that may confound study results (see section "5.3.2 Prohibited Concomitant Therapy" of the protocol): other FVIII concentrate, except for emergency situations*
- Non-compliance issues raised by the investigator or sponsor*EXT
- Dosing errors (less than 80% or more than 120% of the planned dose of *Human-cl rhFVIII (only for the PK phase)*)

- Treatment errors (FVIII concentrate other than *Human-cl rhFVIII* used for BEs, prophylactic treatment or surgery other than for emergency reasons)*EXT
- More than 2 consecutive blood samples missing for PK assessment
- More than 3 post-baseline blood samples missing for PK assessment
- Treatment duration of less than 6 months (–2 weeks) in Prophylactic Treatment—Phase II
- Deviations from prophylactic treatment with *Human-cl rhFVIII*: >20% of prophylactic infusions were not given within the prescribed treatment intervals (± 1 day) of 3 days more than planned or more in the Prophylactic Treatment Phase II*EXT
- Patients who use FVIII treatment that may confound the PK results:
  resulting in baseline FVIII:C level ≥ 0.05 IU/mL

*EXT Respective major protocol deviations also to be identified separately for the Japanese "Sub-study extension phase".

Lists of major and minor protocol deviations will also be included in each of the CSRs.

6 STATISTICAL ANALYSIS

Please refer to section 13 for an overview of tables (marked "T"), listings ("L") and figures ("F"). Two columns in this table list indicate whether the "T", "L" or "F" will be provided for the main and/or the "Sub-study extension phase", respectively.

6.1 Summary Tables

All collected efficacy and safety assessments will be presented by means of descriptive statistics. If not detailed otherwise, the parameters listed below will be tabulated according to the different types of data. The number of patients in the analysis population (N) and the number of patients contributing to each particular summary (n) will be included in every presentation.

- Binary data (whether or not an event has occurred): counts and proportions
- Count data (the frequency of an event in a set time period): rate (count per unit time)
- Continuous data (measurements on a continuous scale, including quasi-continuous variables): arithmetic mean, standard deviation, median, lower and upper quartile, minimum, maximum
- Scales data (Ordinal and Non-ordinal): absolute and relative frequencies

Additional descriptive and exploratory statistics, such as geometric means or confidence intervals, are included as appropriate. If not mentioned otherwise, confidence intervals are to be understood as two-sided, 95% confidence intervals.

Where appropriate, results will be grouped by different patient characteristics, such as bleeding sites or surgery types, as well as in total.

6.2 Figures

Figures will always reference the number of patients contained in the analysis population and the number of observations represented in the graphic. Various types of graphs, including bar charts, scatter plots, line plots, Kaplan-Meier plots, and plots showing means and standard deviations may be used to illustrate the statistical outcome.

6.3 Listings

Listings for the display of individual data summarized in tables and figures will be provided.

6.4 Interim Analysis

No interim analysis is planned for the main study. The analysis of the main study and the analysis of the Japanese "Sub-study extension phase" will be done separately. They are seen as two different studies.

A database snapshot analysis is planned for the Japanese "Sub-study extension phase" at the time of the database lock of the main study. This analysis will be focused on the safety (adverse event) analysis; results will be provided to the Japanese authority.

6.5 Final analysis

The final statistical analysis will be conducted upon successful completion of all database release (DBR) procedures and sign-off of the DBR form; this will be done separately for the main study and for the Japanese "Sub-study extension phase".

6.6 Dropouts

A complete list of dropouts will be presented, including the reason for dropout, the phase of the study (Initial PK phase, Prophylactic Treatment Phase I or II) in which the patient dropped out and the duration of participation in the trial in terms of total days as well as total exposure (IU and IU/kg) to *Human-cl rhFVIII*. This will be done correspondingly for the Japanese "Sub-study extension phase".

6.7 Statistical Analytical Issues

6.7.1 Adjustments for Covariates

Not applicable. In a primary analysis the annual bleeding rates will be compared to half of the annual bleeding rate from the on demand study GENA-01 without adjustment for covariates.

6.7.2 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 the last available weight measurement will be used for calculating the dose per kg body weight needed for calculation of some PK parameters (last observation carried forward).

For the handling of missing FVIII levels with regard to the PK analysis see Chapters 5.1 (PK-PP population).

6.7.3 Multicenter Studies

No by center analysis and no adjustment of the results is planned for center effects due to the low number of patients per center to be expected.

6.7.4 Multiple Comparisons/Multiplicity

The confirmative test for the primary efficacy variable 'annualized total bleeding rate in patients with individual prophylaxis' will be adjusted for a second test on the secondary efficacy variable 'annualized 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 $2 \times \alpha = 0.025$ (1-sided). All other tests and confidence interval results are considered to be exploratory; hence no corrections for multiplicity are done for these methods.

6.7.5 Use of an 'Efficacy Subset' of Patients

Several "efficacy subsets" (per-protocol populations) are defined in Section 5.1. The overview tables of tables, listings, figures (Section 13) provides detail which analyses will be shown also for the secondary populations.

6.7.6 Active-Control Studies Intended to Show Equivalence

Not applicable.

6.7.7 Examination of Subgroups

Subgroups of prophylactic treatment schedules (only main study)

The efficacy of the individually tailored prophylactic treatment will be analyzed for the subgroup of subjects receiving Human-cl rhFVIII 2x/week (or less) in Prophylactic Treatment—Phase II).

Subgroups of Japanese patients (only main study)

The following additional analyses will be performed to meet Japanese regulations:

- 1. Subgroup analyses splitting the study populations in Japanese and Non-Japanese patients in order to describe similarities and/or differences between these two sub-groups of patients and between Japanese and the complete study population
- 2. Additional analyses of the bleeding frequency and adverse events during Prophylactic Treatment Phase I (standard prophylactic schemes)

All these analyses will be descriptive.

Demographic and background variables

The distribution of demographic and background variables will be provided per Japanese /non-Japanese sub-group and in total. This will comprise statistics on age, body height, body weight, body mass index, ABO blood types; Haemophilia Joint Health Score at screening, bleeding frequency during last 6 months before screening, and target joints for bleeding episodes. Statistics to describe the distributions per sub-group and in total will be

- Minimum, 25%- quantile, median, 75%-quantile, maximum, mean and standard deviation for continuous variables
- absolute frequency and percentage for nominal variables and
- both frequency and continuous data analysis for ordinal variables.

Frequency of bleeding episodes

The mean annualized bleeding rate assuming a Poisson distribution for the occurrence of bleeding episodes will be estimated per Japanese/non-Japanese sub-group and in total with 95% confidence intervals as described in SAP Chapter 9.1 for the complete PROPH population. The outcomes are estimates of the mean annualized bleeding rate with 95% confidence intervals. This will be done

- for all patients with data in Prophylactic Treatment Phase I[#],
- separately for Japanese and Non-Japanese patients in Prophylactic Treatment Phase I,
- separately for Japanese and Non-Japanese patients in Prophylactic Treatment Phase II,

[#] The analysis for all patients in PROPH population during Prophylactic Treatment Phase II is the main analysis already described in Chapter 9.1.

The distribution of the monthly and the individualized annualized bleeding rate (ABR) both in Prophylactic Treatment Phase I and II will be provided per Japanese/non-Japanese sub-group and in total overall; for Prophylactic Treatment Phase II also by severity of BE and by joint/no-joint BE. Statistics to describe the distributions per sub-group and in total will be: Minimum, 25%-quantile, median, 75%-quantile, maximum, mean, standard deviation, 95% confidence intervals for the mean (based on the normal distribution assumption).

In case the sample sizes per sub-group will be sufficient to technically perform it, like for the complete PROPH population, an analysis of individual annualized bleeding rates will be performed 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. The outcomes are estimates of the mean individual annualized bleeding rate with 95% confidence intervals. This will be done

- for all patients with data in Prophylactic Treatment Phase I[#],

- separately for Japanese and Non-Japanese patients in Prophylactic Treatment Phase I,
- separately for Japanese and Non-Japanese patients in Prophylactic Treatment Phase II,

[#] The analysis for all patients in PROPH population during Prophylactic Treatment Phase II is the main analysis already described in Chapter 9.1.

Pharmacokinetics

In order to compare pharmacokinetics of *Human-cl rhFVIII* the Japanese/non-Japanese sub-group and the total distribution of the pharmacokinetic parameters will be provided for both one-stage assay and chromogenic assay results. The following parameters will be compared: AUC, $AUC_{norm}^{\#}$, C_{max}, $C_{max,norm}^{\#}$, T_{max}, in-vivo recovery, terminal half-lives, mean residence times, clearance, volume of distribution at steady state. Statistics to describe the distributions per sub-group and in total will be minimum, 25%- quantile, median, 75%-quantile, maximum, mean, standard deviation, geometric mean, 95% confidence intervals for the mean.

[#] norm: normalized by the dosage per kg body weight

Treatment of Bleeding episodes (BEs)

In order to compare the haemostatic efficacy of human-cl rhFVIII in the treatment of bleeding episodes frequency distributions of personal efficacy assessments for the final outcome of the treatment of a BE (assessed by the investigator as either “excellent”, “good”, “moderate” or “none”) will be compared for BEs in the BLEED population between the Japanese, the non-Japanese sub-group and the total. Success rates will be estimated with 95% confidence intervals overall BEs in the BLEED population per Japanese/non-Japanese sub-group and in total, where “Success” is defined as at least “good”.

Adverse events

In order to compare the incidence of adverse events between the Japanese, the Non-Japanese sub-group and the total frequency tables (absolute frequency and percentage of patients) will be provided for

- a summary of adverse events (number of subjects/infusions with any AE, SAE, Severe AE, at least possibly related AE, AEs that begin within 24 hours of end of infusion, AE leading to death, AE leading to discontinuation of study drug),
- the incidence of treatment-emergent adverse events by system organ class and preferred term.

Similar additional analyses will be performed for all patients and divided by Japanese and Non-Japanese sub-group for treatment emergent adverse events occurring during Prophylactic Treatment Phase I and AEs occurring during Prophylactic Treatment Phase II.

7 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The following demographic data will be collected:

- Age, Gender, Ethnic origin

Further baseline characteristics are:

- Height, Weight,
  Derived variable: Body mass index (BMI)= body weight (kg) / (height (m))^2 *EXT
- FVIII activity (IU/mL)*EXT and FVIII inhibitor (Bethesda assay result; BU/mL)*EXT
- Pre-medication with FVIII during 6 months before screening (on demand, prophylaxis, both)
- Concomitant medications*EXT
  Concomitant medication will be coded with the WHO Drug dictionary including ATC classification. The frequencies by ATC level 2 will be tabulated. Furthermore all concomitant medications will be listed in full detail (reported term and WHO Drug code), including the indication (verbatim term and associated MedDRA code (version 17.0 or later)).
- Medical History and physical examination*EXT
- HIV status and CD4 count
- ABO blood type
- Target joints
- Bleeding frequency in the previous 6 months
- History of inhibitors against FVIII
- Haemophilia Joint Health Score ([2] see APPENDIX I: HAEMOPHILIA JOINT HEALTH SCORE– SUMMARY SCORE SHEET, VERSION 2.1)
  The distribution of the Haemophilia Joint Health Score at study entry will be tabulated for the Gait score and the total score. Absolute and relative frequencies of patients with each possible Gait point result will be provided.

All these demographic data and baseline characteristics will be presented in summary and/or frequency tables or will at least be provided in listings according to section 6.1 and as listed in section 13.

*EXT Items marked with "*EXT" will again be documented at screening of the Japanese "Sub-study extension phase".

8 EVALUATION OF TREATMENT COMPLIANCE AND EXPOSURE

8.1 Main study

Pharmacokinetic assessments:

- Date and time of drug infusion will be documented.
- Total dose and dose per kg body weight administered forPK assessments will be summarized (nominal doses and actual doses according to both assays).

Prophylaxis, treatment of BEs and treatment during surgeries: The following will be tabulated and/or summarized:

- Reason for Administration
- Number of Infusions
- Number of Exposure Days
- Total Dose, dose per indication (PK, prophylaxis (also separated for Phase I and Phase II), BEs, surgery, prevention of recurrent bleeding)
- Doses (IU FVIII/kg BW) per indication (PK, prophylaxis (also separated for Phase I and Phase II), BEs, surgery, prevention of recurrent bleeding), doses separated for first 4 and last 2 months in Phase II.

Furthermore the *Human-cl rhFVIII* batches used will be listed for both assays with their potencies in the listings for doses.

Personalized prophylaxis scheme in Prophylactic Treatment—Phase II:

Compliance: Deviations (dose of more than 20 % and time interval between two administrations of more than 24 hours) from the individually tailored prophylaxis scheme will be listed; changes of the scheme documented by the investigator will be taken into account. The number of deviations will be summarized.

The amount of study drug per kg BW administered in Prophylactic Treatment—Phase II per month (30 days) (for prophylaxis, for BEs, and in total) will be compared to the planned amount per month for prophylaxis and to the amount per month used in the final treatment scheme at the completion visit. The amount of study drug per year (365 days) and per week will also be analyzed. In addition, the amount of study drug per kg BW administered in Prophylactic Treatment—Phase II per month (30 days) (for prophylaxis, for BEs, and in total) will be analysed separately for the first 4 and the last 2 months (i.e., period starting with the 4-Month Visit) of Prophylactic Treatment—Phase II.

The median prophylactic dosing interval per patient over the 6 month observation time will be compared to the planned prophylactic dosing interval and to the prophylactic dosing interval used in the final treatment scheme at the completion visit.

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

Prophylaxis, treatment of BEs and treatment during surgeries: The following will be tabulated and/or summarized:

- Reason for Administration
- Number of Infusions

- Number of Exposure Days
- Total Dose, dose per indication (PK, prophylaxis, BEs, surgery, prevention of recurrent bleeding)
- Doses (IU FVIII/kg BW) per indication (prophylaxis, BEs, surgery, prevention of recurrent bleeding).

Furthermore the *Human-cl rhFVIII* batches used will be listed for both assays with their potencies in the listings for doses.

Personalized prophylaxis scheme in Sub-Study Extension Phase:

Deviations (dose of more than 20 % and time interval between two administrations of more than 24 hours) from the prophylaxis scheme as chosen during the last 2 months of the PROPH II phase will be listed; changes of the scheme documented by the investigator will be taken into account. The number of deviations will be summarized.

The amount of study drug per kg BW administered in Sub-Study Extension Phase per month (30 days) (for prophylaxis, for BEs, and in total) will be compared to the planned amount per month for prophylaxis and to the amount per month used in the final treatment scheme at the completion visit. The amount of study drug per year (365 days) and per week will also be analyzed.

The median prophylactic dosing interval per patient in the Sub-Study Extension Phase will be compared to the planned prophylactic dosing interval and to the prophylactic dosing interval used in the final treatment scheme at the completion visit.

9 EVALUATION OF TREATMENT EFFICACY

The primary endpoint of this clinical study is the efficacy of *Human-cl rhFVIII* in prophylaxis regarding the incidence of break-through bleedings as compared to the bleeding frequency in an on demand study. Further secondary endpoints comprise the efficacy in treatment of BEs and in surgical procedures. The efficacy will be evaluated by descriptive statistics.

9.1 Prophylaxis (Prevention of Bleeding episodes)

9.1.1 Main study

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

Hypotheses and test procedures

A confirmative one-sided one-sample Poisson-test will test whether the annualized total bleeding rate in patients with individual prophylaxis is at least 50% below the mean annualized total bleeding rate in the GENA-01 trial (i.e., if it is < 29). For the derivation of the ABR in the GENA-01 trial see below in the Chapter "Use of GENA-01 trial data".

Assumption:

All time periods of prophylactic treatment and all BEs*will be pooled, each over all patients. The results will be denoted as y (number of BEs) and t (the pooled time intervals 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 365.25 days, y weighted by t/d
(d = 365.25 days, t = sum over all observed days) will follow a Poisson distribution.

Definition of time periods of prophylactic treatment (days) per patient:
Time period between End of Prophylactic Phase I Visit (day of start of Prophylactic Treatment—Phase II) until last dose in Prophylactic Treatment—Phase II + actual individual dosing interval or completion visit whatever is first; excluded are time periods between start of treatment for a surgery and re-start of prophylactic treatment after surgery

*** Definition of the number of all BEs:** all BEs here include documented BEs treated with Human-cl rhFVIII, treated with other FVIII, and not treated during the time periods of prophylactic treatment defined above; excluded are bleeding episodes related to surgery between start of treatment for a surgery and re-start of prophylactic treatment after surgery.

Tests on BE rates:

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

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

where λ_{year} represents the annualized rate of BEs per patient through the 6-month efficacy period, assuming a Poisson distribution for the frequency of BEs.The annualized rate (λ_{year}) of BEs will be estimated along with its 2-sided (1-2α) x 100% confidence limits [6] :

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

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

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

This confirmative test will be adjusted for a second test on the secondary efficacy variable 'annualized 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.

Individual annualized bleeding rate

As an additional analysis of bleeding rates the individual annualized bleeding rate will be analyzed 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.

The individual annualized total bleeding rate is estimated as follows:

$ATBR_{i,IP}$ =
365,25 x (number of all documented BEs in patient i 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: $ATBR_{i,IP}$ = individual annualized total bleeding rate of patient i in study GENA-21b (individual prophylaxis scheme)

* Definition of the number of all BEs see above.

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

This will be done for spontaneous (ASBR), traumatic (ATrBR) and all Bes (ATBR).

The distribution of individual annualized bleeding rates will be additionally shown with descriptive statistics.

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.

Secondary Endpoints:

1) Reduction of the annualized *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, 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.

2) Reduction of the annualized 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, 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.

Use of GENA-01 trial data

All analyses for GENA-01 regarding the purpose of the comparison with GENA-21b data have been done with results from the ITT population of the GENA-01 study. The ITT study population is defined in the statistical analysis plans of the study (Version 5 of May 2, 2011) [7] .

The time with on demand treatment is defined as follows: Time between 96h visit after 2nd PK of cross-over part and completion visit.

Note: Other than for the estimation of the annualized bleeding rate in the GENA-21b study time periods after prophylaxis for surgeries have not been subtracted from the on demand time period in the GENA-01 trial, as there would be no clear definition of the time periods to be excluded which are comparable to the time periods excluded from the GENA-21b trial; in GENA-21b the end of the period is defined with the date of restarting the routine prophylaxis. However, not excluding these time periods from the calculation for the GENA-01 trial would only have very minor impact (only two surgeries, one of them of minor severity) and the impact, if any, is conservative with respect to the comparison to GENA-21b, i.e. slightly underestimate the GENA-01 ABR as there were no BEs associated with the surgical interventions.

Calculation of Annual Bleeding Rate for GENA-01:

All time periods of "observed on demand treatment"[#] and all BEs* have been pooled, each over all patients. The two sums are denoted as y (number of BEs) and t (the pooled time intervals in days). Assuming a standard year of 365.25 days, the ABR in GENA-01 is defined as y weighted by t/d (d = 365.25 days, t = sum over all observed days).

[#] **Definition of periods of observed on demand treatment (days) per patient:**
Time between the patient's 96 h visit after the 2nd PK of the cross-over part of the study and the completion visit. Regarding time periods after surgeries see Note above.

*** Definition of the number of all BEs:** all BEs here include documented BEs treated with Human-cl rhFVIII, treated with other FVIII, and not treated during the time periods of observed on demand treatment defined above; other than for the estimation of the annualized bleeding rate in the GENA-21b study time periods after prophylaxis for surgeries will not be subtracted from the on demand time period in the GENA-01 trial (see Note above).

Additional comparative descriptive analyses on bleeding rates for Prophylactic Treatment Phase II and between Prophylactic Treatment Phase II and I

- Bleeding rates (monthly, projected annually) will also be generated separately for the first 4 and the last 2 months of Prophylactic Treatment Phase II:
  Calculation of periods:
  first 4 months: End of Prophylactic Phase I Visit (day of start of Prophylactic Treatment—Phase II) until day before 4 month visit
  last 2 months: day of 4 month visit until last dose in Prophylactic Treatment—Phase II + actual individual dosing interval or completion visit whatever is first.
  (for both periods: exclusions of period due to surgery as above)
- Bleeding rates (monthly, projected annually) will also be generated for prophylactic treatment phase I :
  Calculation of period:
  72h visit after start of PK until End-of-phase I visit – 1 day, minus time periods from start of a treatment for surgery until restart of routine prophylactic treatment)

Additional comparative within-subject analyses on bleeding rates between Prophylactic Treatment Phase II and I

For patients with a minimum observation time of 1 month in each of the two Prophylactic treatment Phases annual bleeding rates per phase will be compared with a within subject analysis:

1) Descriptive analysis of the difference of individual annualized total bleeding rates $Diff_{ATBR,i} = ATBR_{i,IP} - ATBR_{Pi,SP}$

where
$ATBR_{i,IP}$ = individual annualized total bleeding rate of patient in study GENA-21b (individual prophylaxis scheme; phase PROPH2) and
$ATBR_{i,SP}$ = individual annualized total bleeding rate of patient in study GENA-21b (standard prophylaxis scheme; phase PROPH1)

2) Mantel-Haenszel type estimation of the rate ratio ABR_{Proph2} / ABR_{Proph1} with 95% confidence interval as described for paired data in Sumi et al. [9] :

The rate ratio is estimated by

$$\hat{\varphi}_{MH} = \frac{\sum_{i=1}^{n} y_{2i} \cdot t_{1i} / (t_{1i} + t_{2i})}{\sum_{i=1}^{n} y_{1i} \cdot t_{2i} / (t_{1i} + t_{2i})},$$

with

y_{1i}, y_{2i} : number of BEs of patient i in Phase I and Phase II;
t_{1i}, t_{2i}: observation time of patient i during Phase I and Phase II.

Mantel Haenszel 95% confidence limits are given by:

$$\exp\left[\log(\hat{\varphi}_{MH}) \pm z_{0.975} \cdot \sqrt{\hat{V}(\log(\hat{\varphi}_{MH})}\right],$$

with variance estimator:

$$\hat{V}(\log(\hat{\varphi}_{MH}) = \frac{\sum_{i=1}^{n} y_{2i} \cdot t_{1i} \cdot t_{2i} / (t_{1i} + t_{2i})^2}{\left(\sum_{i=1}^{n} y_{2i} \cdot t_{1i} / (t_{1i} + t_{2i})\right) \cdot \left(\sum_{i=1}^{n} y_{1i} \cdot t_{2i} / (t_{1i} + t_{2i})\right)}$$

and $z_{0.975}$ the 97.5%-quantile of the standard normal distribution.

These analyses will be done for all bleeding episodes, only spontaneous BEs and only traumatic BEs.

Pre-study bleeding rate

The number of bleedings episodes during the 6 months before screening is directly documented in the CRF. Monthly and projected annual pre-study bleeding rates will be estimated from this.

Descriptive analyses

The following will be presented following the manners of presentation described in section 6:

- Number of patients treated prophylactically
- Characteristics and number of prophylactic treatments: Treatment pattern, dosage, changes or interruptions in prophylactic treatments
- Median prophylactic dosing interval per patient

- Number of infusions and exposure days. Infusions administered over midnight will only count as exposure day for the day on which the infusion starts.
- Amount of *Human-cl rhFVIII* used (per week, month, year*, exposure days and infusion, and in total), dose in absolute IU FVIII and in IU FVIII/kg. (Prophylactic Treatment Phase I and II, Prophylactic Treatment Phase separated for first 4 months vs. last 2 months)
  In addition the 6-month pre-study consumption of any FVIII drug will be calculated.
  *projected to 1 year
- Individual annualized bleeding rates (GENA-21b and GENA-01).

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

Prophylaxis data and bleeding rates under prophylaxis during the Sub-Study Extension Phase will be analyzed descriptively.

The following will be presented following the manners of presentation described in section 6:

- Number of patients treated prophylactically
- Characteristics and number of prophylactic treatments: Treatment pattern, dosage, changes or interruptions in prophylactic treatments
- Median prophylactic dosing interval per patient
- Number of infusions and exposure days. Infusions administered over midnight will only count as exposure day for the day on which the infusion starts.
- Amount of *Human-cl rhFVIII* used (per week, month, year*, exposure days and infusion, and in total), dose in absolute IU FVIII and in IU FVIII/kg.
  *projected to 1 year
- Individual annualized bleeding rates.

9.2 Treatment of Breakthrough Bleeding Episodes

9.2.1 Main Study

The following will be presented following the manners of presentation described in section 6:

- Number of patients with at least one breakthrough BE during the PT phase.
- Number and rates of BEs[a] (per site and type of BE)
- Type of BE (spontaneous, traumatic, post-operative, other)
- Site of BE

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

- Date and time of occurrence/of noticing and of end of the BE; the duration of the BEs will be calculated and presented as well (by severity and in total).

  Treatment duration for BE = End date/time of BE - start date/time of BE

  If the end time of a BE is missing it will be set to 23:59 of the same day, if the start time of a BE is missing it will be set to 0:00 of same day.
- Severity of the BE (minor, moderate, major, life threatening) by site of BE
- Efficacy assessment by the patient at the end of the BE, together with the investigator in case of on-site treatment (excellent, good, moderate, none).

  Patients who permanently switch to another FVIII product during their study participation[a] will be considered treatment failures, i.e. the efficacy will be imputed to be "none" for each haemostatic efficacy assessment after the switch in the efficacy analyses.

  There will be two exceptions when patients who switch to another FVIII product during their study participation will **not** be considered treatment failures in the efficacy analyses:

  1. If the administration of another FVIII concentrate was due to an emergency situation (example: accident requiring treatment with FVIII without patient (or ICU personnel) having access to IMP product)
  2. If the IMP was not available for the patient in time (example: patient experiences severe BE but has not enough product available at home).

  These patients may stay in the study until they have reached the minimum of 6 months observational period.
  The efficacy assessment for a BE treated completely with a different FVIII due to one of these exceptions will not be evaluated for the efficacy of *Human-cl rhFVIII* (missing efficacy assessement).
  In case the BE was treated partly with *Human-cl rhFVIII* and partly with another FVIII because of *one of the exceptions*, the efficacy of *Human-cl rhFVIII* in this BE cannot be rated and is set to missing assessment.
  In case the BE was treated partly with *Human-cl rhFVIII* and partly with another FVIII because of *other reasons* than described in the exceptions the efficacy of *Human-cl rhFVIII* in this BE cannot be rated better than "moderate", i..e. if the investigator rated the efficacy as excellent, good or moderate the efficacy is set to "moderate", if the investigator rated it as "poor" it remains "poor".
- In addition to the four point scale the proportion of BEs successfully treated with *Human-cl rhFVIII* will be evaluated for all BEs as well as for BEs of different severity. "Successfully treated" are all "excellent" and "good" efficacy ratings of treated BEs.
  The rate of successfully treated BEs (all BEs, spontaneous BEs, traumatic BEs) will be provided with a 95% exact confidence interval.
- In a secondary analysis the frequency of successfully treated BEs will be analyzed with a GEE (Generalized Estimation Equations) 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.
- Treatment details: number of exposure days, number of infusions, dosing incl. batch numbers., consumption of *Human-cl rhFVIII* (IU in total, IU/kg per month, per year, per BE)

Any haemostatic co-medication will be listed.

[a] Subjects will be excluded from the PP and the PROPH-PP population

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

Variables are documented and presented like in the main study (except confidence intervals on success rates and GEE analysis). Calculations and data handling will be performed like in the main study.

9.3 Haemostatic control in Surgical Procedures

9.3.1 Main study

The following will be presented following the manners of presentation described in section 6:

- Number of patients undergoing surgeries (minor, major, total)
- Number of surgeries, overall (minor, major, total)
- Surgery characteristics (Type and site, pre-planned or emergency, reason, severity, duration, average and maximal expected blood loss for the planned surgical procedure and for the same procedure in a patient with normal haemostasis and of the same sex, age, and stature, patient's body weight)
- Details on treatment for surgical prophylaxis (number of exposure days and infusions prior to surgery, dosing details, total amount of *Human-cl rhFVIII*)
- Details on treatment with *Human-cl rhFVIII* during and post the surgical procedure (number of infusions, dosing details amount of trial product)
- Pre-, intra-, and post-operative FVIII plasma levels
- Details on concomitantly administered products at any time prior, during or post the surgical procedure including any blood/blood product transfusions but excluding drugs given for routine anaesthesia.
- Efficacy evaluation
  - by the surgeon at the end of the surgery (see scale with predefined criteria in Section 3.5.6.5),
  - by the haematologist at the end of the postoperative period (see scale with predefined criteria in Section 3.5.6.5), and
  - jointly by surgeon and haematologist an overall efficacy assessment at the end of the postoperative period (last post-operative day) (scale (without any predefined criteria).

  Patients who switch to another FVIII product during a surgery* will be considered treatment failures, i.e. the efficacy will be imputed to be "none" for each haemostatic efficacy assessment after the switch in the efficacy analyses for this surgery. Exception: Not enough *Human-cl rhFVIII* study drug was available at the site; in this case the efficacy will be considered a missing value with regard to *Human-cl rhFVIII.*
  * Surgeries will be excluded from the SURG-PP population.
- Expected (average and maximum) and actual blood loss and difference between planned and actual blood loss
- Expected and actual duration of the surgical procedure and difference between expected and actual duration
- Any wound hematomas and whether they require surgical evacuation

- Laboratory tests: haematology and clinical chemistry (before and optionally on any post-operative day until patient returns to regular prophylaxis)
- Vital signs (pre- intra- and postoperatively)

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

Variables are documented and presented like in the main study. Calculations and data handling will be performed like in the main study.

9.4 Assessment of the correlation of vWF antigen concentration and Human-cl rhFVIII half-life (only main study)

vWFAg data will be analysed descriptively per time point. Pre-PK values of vWFAg will be correlated with the terminal half-life resulting from the subsequent PK analysis (both assays); both Pearson's correlation coefficient and Spearman's rank correlation coefficient will be presented. The descriptive statistics of vWFAg concentration will be presented by ABO type.

9.5 Assessment of the association of ABO blood type and Human-cl rhFVIII half-life (only main study)

The descriptive statistics of terminal half-lives will be presented by ABO type.;

10 EVALUATION OF PHARMACOKINETICS (ONLY MAIN STUDY)

For each patient one full FVIII pharmacokinetic profile with *Human-cl rhFVIII* will be generated in the initial PK evaluation phase. The analysis will be done with Pharsight Phoenix® WinNonlin ®, Version 6.3 or later [1] . The analysis will be done
- sequentially when the data (only one-stage assay analyses) of a new patient arrives from the central lab. This calculation will be the basis for a recommendation of individual prophylactic treatment schedule in Prophylactic Treatment—Phase II. See Chapter 10.1.1.1 .
- summarized for all PK data on both assays at the final analysis based on an electronic data transfer from the central lab.

Pharmacokinetic parameters will be determined from plasma FVIII levels (FVIII:C) before (within 1 hour) and at 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 infusion of 60 ± 5 IU/kg (labelled potency) of *Human-cl rhFVIII*. Time windows refer to the accepted time frame for sampling; FVIII levels resulting from samples outside the time windows will not be included into summary statistics of FVIII levels per time point, However, all values will be included into the PK evaluations; all calculations (except T_{max}) will be based on the actual sampling times and not on nominal time points. FVIII:C values below the limit of quantification (<0.009 IU/mL) will be set to 0 or to 0.0045 IU/mL for PK calculations depending on the fit to the data. Calculation of pharmacokinetic parameters and dosing calculations will be based on the actual potency for the used product

The following parameters will be calculated for all patients:

Dact	Actual dose (IU/kg) (based on real potency of specific batch in PK analysis as measured by central lab)	D_{act} = D_{nom} x (Actual Potency/Labelled Potency)where D_{nom} stands for the nominal Dose according to the product label per kg body weight.
Cmax	Peak concentration observed (IU/mL)	up to the 3 hour measurement after end of the infusion
Cmax,norm	Observed peak concentration normalised for the dose given ((IU/mL)/(IU/kg))	$C_{\max,norn} = \frac{C_{\max}}{D_{act}}$
Tmax	Time when Cmax is observed (h)	Timing starts at end of infusion
IVR	In vivo incremental recovery	will be determined from the FVIII level before the infusion and the peak level after the infusion of Human-cl rhFVIII by $IVR((IU/mL)/(IU/kg)) = \frac{(C_{\max} - C_{pre})}{D_{act}} \cdot 100$ where C_{pre} is the baseline FVIII level before administration of study drug and D_{act} is the dose according to the actual potency of the FVIII concentrate

In case a *one-compartment model* is appropriate the following pharmacokinetic parameters will be estimated:

V	Volume of distribution of central compartment (mL/kg)	*
k_{10}	Elimination rate	slope of the regression line, *
C_0	Concentration at end of injection (IU/mL)	$C_0 = D_{act}/V$; intercept (t=0) of regression curve
$t_{1/2}$	Elimination half-life (h)	$t_{1/2} = \log(2)/k_{10}$
AUC	Area under the curve from baseline to infinity (h xIU/mL)	$AUC = \int_0^\infty C(t) \cdot dt$
CL	Clearance (mL/h/kg)	$CL = D_{act}/AUC$
AUMC	Area under the moment curve (from baseline to infinity) (h2 x IU/mL)	$AUMC = \int_0^\infty t \cdot C(t) \cdot dt$
MRT	Mean residence time (h)	$MRT = \frac{AUMC}{AUC}$
V_{ss}	Volume of distribution at steady state (mL/kg)	$V_{SS} = CL \cdot MRT$

* Estimated parameters from non-linear regression according to the model equation, all other parameters derived as secondary parameters (Model 1: One compartment with bolus input and first-order output in Phoenix User's guide [1])

In case a *two-compartment model* is appropriate the following pharmacokinetic parameters will be estimated:

$V=V_1$	Volume of distribution of central compartment (mL/kg)	*
k10	Elimination rate	*
k12	Transfer rate central to peripheral compartment	*
k_{21}	Transfer rate peripheral to central to compartment	*
α, β	Regression coefficients associated with distribution and elimination phase	*
α-half life	Initial half-life (h) (distribution phase)	$t_{1/2,init} = \log(2)/\alpha$
β-half life	Terminal half-life (h) (elimination phase)	$t_{1/2,term} = \log(2)/\beta$

AUC	Area under the curve from baseline to infinity (h x IU/mL)	$AUC = \int_0^\infty C(t) \cdot dt$
CL	Clearance (mL/h/kg)	CL= D_{act} /AUC
AUMC	Area under the moment curve (from baseline to infinity) (h2 x IU/mL)	$AUMC = \int_0^\infty t \cdot C(t) \cdot dt$
MRT	Mean residence time (h)	$MRT = \frac{AUMC}{AUC}$
V_{ss}	Volume of distribution at steady state (mL/kg)	$V_{SS} = CL \cdot MRT$

* Estimated parameters from non-linear regression according to the model equation, all other parameters derived as secondary parameters (Model 7: two-compartment model with bolus input and first-order output with micro-constants as primary parameters in Phoenix user guide [1])

All these parameters will be listed. The following parameters will be summarized in Tables including mean and standard deviation, median, range, geometric mean and the associated geometric standard deviation and 95%-confidence intervals:

D_{act}, C_{max}, $C_{max,norm}$, T_{max}, IVR, $t_{1/2}$, α-half life (only two-compartment model), AUC, CL, MRT, V_{ss}.

Summarizing plots of the FVIII concentrations will show mean and standard deviations per assay and per scheduled time point in the final analysis.

10.1.1.1 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 the sponsor.

One- compartment model

If the PK elimination curve shows a one phase decay dose and time interval will be calculated in the following way:

From the plasma concentration-time curve function

(1) $C(t) = C_0 \cdot e^{-k_{10}t}$,

with C(t) concentration of FVIII:C at t hours after injection, C_0 maximum concentration at time of injection (equal to dose (IU/kg) / V volume of distribution), k_{10} elimination coefficient (=log(2)/ half life ($t_{1/2}$)), one can derive D(τ), the single dose per IU/kg of Human-cl rhFVIII to be administered so that the elimination curve decreases to C(τ) at time τ, by

(2) $D(\tau) = V \cdot C(\tau) \cdot e^{(\log(2)\cdot\tau/t_{1/2})}$,

where τ (hours) is the earliest expected time when C(t) decreases to C(t) ≤ 0.01 IU/mL, C(τ) = 0.01 IU/mL. V volume of distribution (ml/kg), $t_{1/2}$ half-life (hours) are derived from each patient's initial PK data.

From this one also can derive

(3) $\tau = t_{1/2} \cdot \log(\frac{D(\tau)}{V} \cdot 100) / \log(2)$,

as a formula for time interval between two prophylactic treatments assuming that the level of elimination curve has decreased to 0.01 at τ. *Note:* the number "100" here is derived from 1/0.01.

An alternative formula for (2) can be derived from Bjoerkman et al. [8] :

(4) $D(\tau) = 100 \cdot \frac{C(\tau)}{IVR} \cdot e^{\log(2)\tau/t_{1/}} \cdot (1 - e^{-\log(2)\cdot\tau/t_{1/2}})$,

When assuming that there is no accumulation by multiple dosing as C(τ)=0.01 and V ≤100 mL/kg (IVR ≥ 1) (4) simplifies to

(4') $D(\tau) \approx 100 \cdot \frac{C(\tau)}{IVR} \cdot e^{\log(2)\tau/t_{1/}}$, with (4) – (4') ≤ 1 IU/kg

which is very similar to (2) as when there is a baseline level of 0 before administration

(5) $\frac{IVR}{100} = \frac{C_{max}}{D} \approx \frac{C_0}{D} = \frac{1}{V}$.

Both (2) and (4') will be calculated for a range of values τ resulting in D(τ) between 10 and 80 IU/kg under the condition that C_0<2.0 IU/mL .

Two- compartment model

If the PK elimination curve shows two different phases of decay dose and time interval will be calculated in the following way:

From the plasma concentration-time curve function for a two-compartment model with bolus input and first-order output with micro-constants as primary parameters (representation given as Model 7 in Phoenix user guide [1])

(6) $$C(t) = A \cdot \exp(-\alpha \cdot t) + B \cdot \exp(-\beta \cdot t),$$

with A= $\frac{D}{V} \cdot \frac{(\alpha - k_{21})}{(\alpha - \beta)}$, B= $-\frac{D}{V} \cdot \frac{(\beta - k_{21})}{(\alpha - \beta)}$,

C(t) concentration of FVIII:C at t hours after injection, D dose (IU/kg), V=V_1 volume of distribution, central compartment, α macro rate constant associated with the distribution phase, β macro rate constant associated with the elimination phase, k_{21} transfer rate from peripheral to central compartment,
one can derive D(τ), the single dose of Human-cl rhFVIII to be administered so that the elimination curve decreases to C(τ) at time τ, by

(7) $$D(\tau) = V_1 \cdot C(\tau) \cdot M(t),$$

with M(t)= $(\alpha - \beta) / \left[(\alpha - k_2) \cdot e^{-\alpha \cdot t} + (\beta - k_2) \cdot e^{-\beta \cdot t} \right]$

where τ (hours) is the earliest expected time when C(t) decreases to C(t) ≤ 0.01 IU/mL, C(τ) = 0.01 IU/mL.

V_1 volume of distribution (ml/kg) for central compartment, α, β, k_{21} (see above) are derived from each patient's initial PK data.

Formula (7) will be calculated for a range of values τ resulting in D(τ) between 40 and 100 IU/kg under the condition that C_0<2.0 IU/mL.

In case of numerical or other issues for the calculations of (7) the recommendations for the prophylactic treatment schedule will be supported by additional simulations of multiple dose administrations in Phoenix.

Summary and recommendation to be sent to sponsor

For each patient a list of the calculated PK parameters, a graph of the elimination curve and a tabulation of one or several options resulting from the above calculations will be sent to the sponsor as a basis for the decision on the individual prophylactic treatment schedule in Prophylactic Treatment—Phase II.

11 EVALUATION OF SAFETY PARAMETERS

11.1 Adverse Events

11.1.1 Main study

All treatment emergent adverse events will be displayed in summary tables and listings. Treatment emergent AEs are those starting between first use of Human-cl rhFVIII and final assessment, or starting before first use of Human-cl rhFVIII and worsening after start of first use of Human-cl rhFVIII (including events likely to be related to the underlying disease except BEs* not considered as serious AE, or a concomitant illness or medication). All other documented AEs are considered as not treatment emergent; they will be displayed in a separate listing.

* The occurrence and outcome of BEs are analyzed in the respective efficacy analyses.

Incidences of adverse events will be given as numbers and percentages of patients; for AEs judged to be related to study drug or occurring during or within 24 hours of the end of an infusion also the numbers and percentages of infusions associated with such AEs will be presented:

- Any AE (by MedDRA (version 17.0 or later) preferred term (descending frequency) and by MedDRA System Organ Class (SOC))
- Any serious AE (by MedDRA System Organ Class (SOC)/ preferred term)
- Any AE probably or possibly related to the IMP (by MedDRA System Organ Class (SOC)/ preferred term)
- Any AE that begins within 24 hours after the end of an injection[a] (by MedDRA preferred term (descending frequency) and by MedDRA System Organ Class (SOC))
- Any severe AE (by MedDRA System Organ Class (SOC)/ preferred term)
- Any withdrawal due to AE

Summary tables for AEs will be given by SOC and preferred term. Additionally, AEs will be summarized by severity and relationship to study treatment. These summary tables will feature total counts and percentages, prior exposure days to *Human-cl rhFVIII* , total amount of *Human-cl rhFVIII* used prior to the AE. Details of AEs will be provided in individual listings to evaluate the need of further investigation of any apparent pattern or trend in AE rates.

The MedDRA coded terms and the corresponding original terms used by the investigator will be listed.

All adverse events for each patient will be listed in Appendix 16 of the CSR, featuring the following data:

- Patient identifier and characteristics (age, sex, weight)
- The adverse event (preferred term, reported term)
- Onset, date of resolution and duration of the adverse event
- Severity (mild, moderate, severe)
- Seriousness (serious/non-serious)
- Action taken - General (none, drug therapy, tests performed, other) and on study drug (none, drug withdrawn, dose reduced, dose increased)
- Outcome (recovered, recovering, not recovered, recovered with sequelae, fatal, unknown)

[a] In case another infusion starts within the 24 hours the AE will be related to the last infusion.

- Causality assessment (probable, possible, unlikely, not related)
- Study treatment (with prophylactic treatment schedule) at time of event or most recent study treatment taken, including dose and batch number
- Previous exposure to *Human-cl rhFVIII* (exposure days and total amount used)

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

Variables are documented and presented like in the main study, if applicable. Calculations and data handling will be performed like in the main study.

AEs that start in the main study and still are ongoing when the extension study starts belong to the main study. Only, if they worsen during the extension study they are counted as a new AE also for the extension study. AEs that start between the completion visit of the main study and the screening for the extension study, if any, are counted in the extension study, if the patient is included into the extension study.

11.2 Laboratory Data

11.2.1 Main Study

Routine laboratory parameters are planned to be investigated only at the screening visit for all patients and within 12 hours before start of a surgery and optionally on any post-operative day until patient returns to regular prophylaxis in case of surgeries. They will be listed for all patients, using indicators for values outside the associated reference ranges. Laboratory parameters will be tabulated, and the sample characteristics will be presented by time point. In addition for surgeries statistics on the changes from baseline (i.e., before surgery) will be provided.

All laboratory parameters will be listed with their associated units and normal reference ranges.

All recorded determinations of FVIII:C plasma levels during Prophylactic Treatment Phase II will be listed together with the time since last administration of *Human-cl rhFVIII.*

All recorded determinations of inhibitors against FVIII will be listed. If any, the occurrence and cumulative incidence of inhibitors (inhibitor titter ≥ 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 summarized in a shift table.

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

Routine laboratory parameters are planned to be investigated only within 12 hours before start of a surgery and optionally on any post-operative day until patient returns to regular prophylaxis in case of surgeries. They will be listed by time point for all surgeries, using indicators for values outside the associated reference ranges. In addition the changes from baseline (i.e., before surgery) will be provided.

All recorded determinations of FVIII:C plasma levels will be listed together with the time since last administration *Human-cl rhFVIII.*

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 summarized in a shift table.

11.3 Vital Signs

11.3.1 Main Study

Blood pressure (systolic/diastolic), pulse, and body temperature will only be documented on baseline, during PK (pre-infusion, one and 72 hours after infusion) and for surgeries. Descriptive statistics will be provided per time point; values will be tabulated, and the sample characteristics will be presented by time point.

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

Blood pressure (systolic/diastolic), pulse, and body temperature will only be documented for surgeries as in the main study. Values will be listed.

11.4 Physical Examination

11.4.1 Main Study

All abnormal findings from the physical examination will be listed. Shift tables will be prepared for the assessments (normal/abnormal) of each body system and in total.

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

Variables are documented and presented like in the main study.

12 REFERENCES

[1] Phoenix® WinNonlin® 6.3, Connect 1.3, and NLME 1.2 copyright ©2005-2012, Certara, L.P.

[2] Feldman BM, Funk S, Hilliard P, Van Der Net J, Zourikian N, Berstrom B-M, Engelbert RHH, Abad A, Petrini P, Manco-Johnson M, and the International Prophylaxis Study Group (Authors/developers): Hemophilia Health Score (HJHS 2.1).

[3] Octapharma: GENA-01 report "Clinical Study To Investigate The Pharmacokinetics, Efficacy, Safety And Immunogenicity Of Human-cl rhFVIII, A Newly Developed Human Cell-Line Derived Recombinant FVIII Concentrate In Previously Treated Patients With Severe Haemophilia A.", Version 01, 15 February 2013

[4] Octapharma: GENA-08 report "Clinical Study To Investigate The Efficacy, Safety, And Immunogenicity Of Human-cl rhFVIII In Previously Treated Patients With Severe Haemophilia A", Version 01, 19-July-2012

[5] Octapharma: GENA-09 report "Clinical Study to Investigate the Pharmacokinetics, Efficacy, Safety and Immunogenicity of Human-cl rhFVIII in Previously Treated Patients with Severe Haemophilia A", 14-December-2010

[6] Johnson NL, Kotz S (Ed): Discrete distributions, Wiley, New York 1969

[7] Statistical Analysis Plan: GENA-01 Clinical Study To Investigate The Pharmacokinetics, Efficacy, Safety And Immunogenicity Of Human-cl rhFVIII, A Newly Developed Human Cell-Line Derived Recombinant FVIII Concentrate In Previously Treated Patients With Severe Hemophilia A, Octapharma AG, Version 5.0, 2-May-2011

[8] Björkman S, Blanchette VS,_ Fischer K, Oh M, Spotts G, Schroth P, Fritsch S, Patrone L, Ewenstein BM, for the ADVATE Clinical Program Group, and Collins PW : Comparative pharmacokinetics of plasma- and albumin-free recombinant factor VIII in children and adults: the influence of blood sampling schedule on observed age-related differences and implications for dose tailoring, Journal of Thrombosis and Haemostasis, 8: 730–736, 2010

[9] Sumi M, Tango T: Inference on the rate ratio of recurrent events for the matched pairs design, Statistics in Medicine, 29: 3186-3193, 2010

13 TABLES, FIGURES AND LISTINGS (SECTION 14 AND 16.2 OF THE CSR)

The following tables, figures and listings (TLFs) will be generated.
As most TLFs for the "Sub-study Extension Phase" have the same design as the respective TLFs in the main study the combined list indicates whether the respective TLF will be generated for the main study and/or for the "Sub-study Extension Phase".

All output will be headed with an appropriate heading specifying study ID and title; output for the Japanese "Sub-study Extension Phase" will have an additional heading "Sub-study Extension Phase".

All output will be dated and have page numbers in the form 'Page x of y' separately for the main study and for the "Sub-study Extension Phase".

The order and numbering of the various parts of the Clinical Study Reports may not necessarily follow the scheme used below.

All statistical output will identify the underlying analysis populations (see section 5), and indicate the number of patients/ events in this population (N) and the number of patients/events actually contributing to the particular output (n).

T/L/F: "T": table, "L" listing, "F" figure, "A" Appendix. "All" in Population column: all populations referring to patients.

No.	T/ L/ F	*Title*	Population	Main study	Japan."Sub -Study Ext. Phase"
		Tables section 14.1-3			
		Analysis populations			
14.1.1.1	T	Subject disposition and analysis populations *Number of patients enrolled, erroneously enrolled, treated, completed, withdrawn*	All	X	X
14.1.1.2	T	Bleeding episodes analysis populations	All bleedings	X	X
14.1.1.3	T	Surgery analysis populations	All surgeries	X	X

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.1.2.1	T	Protocol deviations – Major *Frequency of protocol populations*	SAF, PP	X	X
14.1.2.2	T	Protocol deviations – Major *Frequency of protocol populations*	SAF, PP	X	X
14.1.3.1	T	Compliance to schedule of PK assessments - ITT population *Counts of PK assessments (not) performed according to the schedule*	ITT	X	-
14.1.3.2	T	Compliance to schedule of PK assessments - PK-PP population *Counts of PK assessments (not) performed according to the schedule*	PK-PP	X	-
14.1.4	T	Number of subjects per center and analysis population	SAF	x	x
		Demographic Data Summary Tables			
14.1.5	T	Statistics on age, body height, body weight, body mass index, ethnicity, ABO blood types	SAF	X	X
14.1.5J	T	Statistics on age, body height, body weight, body mass index, ethnicity, ABO blood types - Japanese Subgroup Analysis	J/NJ	X	-
14.1.6	T	Statistics on study participation (duration of treatment, EDs)	SAF	X	X
14.1.8	T	FVIII activity (baseline) and Bethesda assay results at initial PK visit	SAF	X	-
14.1.9	T	Hemophilia joint health score (Version 2.1) before screening	SAF	X	
14.1.9J	T	Hemophilia joint health score (Version 2.1) before screening - Japanese Subgroup Analysis	J/NJ	X	-
14.1.10.1	T	Bleeding frequency during last 6 months before screening	ITT, PP, SAF, PROPH, PROPH-PP	X	-
14.1.10.1J	T	Bleeding frequency during last 6 months before screening - Japanese Subgroup Analysis	J/NJ	X	-
14.1.10.2	T	Bleeding frequency during last 6 months before screening for subjects with (only) on demand treatment (per 6 month, recalculated per month, annualized individual bleeding rate)	ITT, PP, SAF, PROPH, PROPH-PP	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.1.10.3	T	Bleeding frequency during last 6 months before screening for subjects with (any) prophylactic treatment (per 6 month, recalculated per month, annualized individual bleeding rate)	ITT, PP, SAF, PROPH, PROPH-PP	X	-
14.1.11.1	T	Frequency of use of prior medications (within 1 month before screening) by ATC class (without surgeries)	ITT, SAF	X	-
14.1.11.2	T	Frequency of use of concomitant medications by ATC class (without surgeries)	ITT, SAF	X	X
14.1.12	T	Previous treatment of hemophilia A (During the last 6 months before study entry) - overall and by prophylaxis/on demand treatment	ITT, SAF	X	-
14.1.13	T	Amount of previous treatment of hemophilia A with FVIII (During the last 6 months before study entry) - overall and by prophylaxis/on demand treatment	ITT, SAF	X	-
14.1.14	T	Statistics on target joints for bleeding episodes	ITT, PP, SAF, PROPH, PROPH-PP	X	-
14.1.14J	T	Statistics on target joints for bleeding episodes - - Japanese Subgroup Analysis	J/NJ	X	-
		Efficacy Data Summary figures, tables and listings			
		Prophylactic treatment X* in Column “Japan. Sub-Study Extension Phase”: “Prophylactic Treatment Phase II” to be replaced by “Japanese Sub-Study Extension Phase” X** in Column “Japan. Sub-Study Extension Phase”: “Prophylactic Treatment Phase I and II” to be replaced by “Japanese Sub-Study Extension Phase”			
14.2.1	T	Compliance to prophylaxis schedule, Prophylactic Treatment Phase I	ITT	X	-
14.2.2	T	Compliance to prophylaxis schedule, Prophylactic Treatment Phase II	PROPH	X	X*
14.2.3.1	T	Statistics on the number of exposure days for prophylactic treatment to Human-cl rhFVIII and dosages administered, Prophylactic Treatment Phase I	ITT	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.2.3.2.1	T	Statistics on the number of exposure days for prophylactic treatment to Human-cl rhFVIII and injections administered, Prophylactic Treatment Phase II	PROPH, PROPH-PP	X	X*
14.2.3.2.2	T	Statistics on the number of exposure days for prophylactic treatment to Human-cl rhFVIII and injections administered, first 4 months of Prophylactic Treatment Phase II	PROPH, PROPH-PP	X	-
14.2.3.2.3	T	Statistics on the number of exposure days for prophylactic treatment to Human-cl rhFVIII and dosages administered, last 2 months of Prophylactic Treatment Phase II	PROPH, PROPH-PP	X	-
14.2.3.3	T	Statistics on the number of exposure days for prophylactic treatment to Human-cl rhFVIII and injections administered, All prophylactic treatment	PROPH, PROPH-PP	X	-
14.2.4.1.1	T	Statistics on the amount of Human-cl rhFVIII (IU) for prophylactic treatment per week, per month, per year, per exposure days, per injection and in total, Prophylactic Treatment Phase I	ITT	X	-
14.2.4.1.2.1	T	Statistics on the amount of Human-cl rhFVIII (IU) for prophylactic treatment per week, per month, per year, per exposure days, per injection and in total, Prophylactic Treatment Phase II	PROPH, PROPH-PP	X	X*
14.2.4.1.2.2	T	Statistics on the amount of Human-cl rhFVIII (IU) for prophylactic treatment per week, per month, per year, per exposure days, per injection and in total, first 4 months of Prophylactic Treatment Phase II	PROPH, PROPH-PP	X	-
14.2.4.1.2.3	T	Statistics on the amount of Human-cl rhFVIII (IU) for prophylactic treatment per week, per month, per year, per exposure days, per injection and in total, last 2 months of Prophylactic Treatment Phase II	PROPH, PROPH-PP	X	-
14.2.4.1.3	T	Statistics on the amount of Human-cl rhFVIII (IU) for prophylactic treatment per week, per month, per year, per exposure days, per injection and in total, All prophylactic treatment	PROPH, PROPH-PP	X	-
14.2.4.2.1	T	Statistics on the dosage of Human-cl rhFVIII (IU/kg) for prophylactic treatment per week, per month, per year, per exposure days, per injection and in total, Prophylactic Treatment Phase I	ITT	X	-
14.2.4.2.2.1	T	Statistics on the dosage of Human-cl rhFVIII (IU/kg) for prophylactic treatment per week, per month, per year, per exposure days, per injection and in total, Prophylactic Treatment Phase II	PROPH, PROPH-PP	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.2.4.2.2. 1.1	T	Statistics on the dosage of Human-cl rhFVIII (IU/kg) for prophylactic treatment per week, per month, per year, per exposure days, per injection and in total, Prophylactic Treatment Phase II – Dosing scheme with dosing freq <=2/wk	PROPH, PROPH-PP	X	-
14.2.4.2.2. 1.2	T	Statistics on the dosage of Human-cl rhFVIII (IU/kg) for prophylactic treatment per week, per month, per year, per exposure days, per injection and in total, Prophylactic Treatment Phase II – Dosing scheme with dosing freq >2/wk	PROPH, PROPH-PP	X	-
14.2.4.2.2. 2	T	Statistics on the dosage of Human-cl rhFVIII (IU/kg) for prophylactic treatment per week, per month, per year, per exposure days, per injection and in total, first 4 months of Prophylactic Treatment Phase II	PROPH, PROPH-PP	X	-
14.2.4.2.2. 2.1	T	Statistics on the dosage of Human-cl rhFVIII (IU/kg) for prophylactic treatment per week, per month, per year, per exposure days, per injection and in total, first 4 months of Prophylactic Treatment Phase II – Dosing scheme with dosing freq <=2/wk	PROPH, PROPH-PP	X	-
14.2.4.2.2. 2.2	T	Statistics on the dosage of Human-cl rhFVIII (IU/kg) for prophylactic treatment per week, per month, per year, per exposure days, per injection and in total, first 4 months of Prophylactic Treatment Phase II – Dosing scheme with dosing freq >2/wk	PROPH, PROPH-PP	X	-
14.2.4.2.2. 3	T	Statistics on the dosage of Human-cl rhFVIII (IU/kg) for prophylactic treatment per week, per month, per year, per exposure days, per injection and in total, last 2 months of Prophylactic Treatment Phase II	PROPH, PROPH-PP	X	-
14.2.4.2.2. 3.1	T	Statistics on the dosage of Human-cl rhFVIII (IU/kg) for prophylactic treatment per week, per month, per year, per exposure days, per injection and in total, last 2 months of Prophylactic Treatment Phase II – Dosing scheme with dosing freq <=2/wk	PROPH, PROPH-PP	X	-
14.2.4.2.2. 3.2	T	Statistics on the dosage of Human-cl rhFVIII (IU/kg) for prophylactic treatment per week, per month, per year, per exposure days, per injection and in total, last 2 months of Prophylactic Treatment Phase II – Dosing scheme with dosing freq >2/wk	PROPH, PROPH-PP	X	-
14.2.4.2.3	T	Statistics on the dosage of Human-cl rhFVIII (IU/kg) for prophylactic treatment per week, per month, per year, per exposure days, per injection and in total, All prophylactic treatment	, PROPH, PROPH-PP	X	X*
14.2.5.1	T	Prophylactic treatment phase I: Individual annualized total bleeding rates by severity of bleeding events and overall	PROPH, PROPH-PP	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.2.5.1J	T	Prophylactic treatment phase I: Individual annualized total bleeding rates by severity of bleeding events and overall – Japanese Subgroup Analysis	J/NJ	X	-
14.2.5.2	T	Prophylactic treatment phase I: Individual annualized total bleeding rates - by spontaneous/traumatic bleedings and overall	PROPH, PROPH-PP	X	-
14.2.5.2J	T	Prophylactic treatment phase I: Individual annualized total bleeding rates - by spontaneous/traumatic bleedings and overall – Japanese Subgroup Analysis	J/NJ	X	-
14.2.5.3	T	Prophylactic treatment phase I: Individual annualized total bleeding rates - by joint / non-joint bleedings and overall	PROPH, PROPH-PP	X	-
14.2.5.3J	T	Prophylactic treatment phase I: Individual annualized total bleeding rates - by joint / non-joint bleedings and overall – Japanese Subgroup Analysis	J/NJ	X	-
14.2.6.1.1	T	Statistics on the dosage of Human-cl rhFVIII (IU/kg) for prophylactic treatment and BEs in Prophylactic Treatment Phase I and II compared to the starting treatment scheme and the final treatment scheme in Prophylactic Treatment Phase II – Actual dosing	PROPH, PROPH-PP	X	X**
14.2.6.1.2	T	Statistics on the dosage of Human-cl rhFVIII (IU/kg) for prophylactic treatment in Prophylactic Treatment Phase I and II compared to the starting treatment scheme and the final treatment scheme in Prophylactic Treatment Phase II – Actual dosing	PROPH, PROPH-PP	X	X**
14.2.6.1.3	T	Statistics on the dosage of Human-cl rhFVIII (IU/kg) for BEs in Prophylactic Treatment Phase I and II compared to the starting treatment scheme and the final treatment scheme in Prophylactic Treatment Phase II – Actual dosing	PROPH, PROPH-PP	X	X**
14.2.6.2	T	Statistics on the dosage of Human-cl rhFVIII (IU/kg) for prophylactic treatment in Prophylactic Treatment Phase I and II compared to the starting treatment scheme and the last treatment scheme in Prophylactic Treatment Phase II – Planned dosing	PROPH, PROPH-PP	X	X**
14.2.7	T	Prophylactic treatment phase II: Statistics on dosing intervals (planned, first, last, median), median prophylactic dosing interval	PROPH, PROPH-PP	X	X*
14.2.8.1	T	Prophylactic treatment phase II: Planned weekly consumption of Human-cl rhFVIII (IU/kg) for prophylaxis.	PROPH, PROPH-PP	X	X*
14.2.8.2	T	Prophylactic Treatment phase II: frequency of first and last dosing schemes	PROPH, PROPH-PP	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.2.9.1	T	Prophylactic treatment phase II: basic summary statistics on prophylactically treated subjects: Number of changes per patients from visit to visit in planned prophylactic treatment	PROPH, PROPH-PP	X	X*
14.2.9.2	T	Prophylactic Treatment phase II: basic summary statistics on prophylactically treated subjects: Number of changes per patient in actual prophylactic treatment compared to planned treatment schedule	PROPH, PROPH-PP	X	X*
14.2.10	T	Prophylactic treatment phase II: Individual annualized total bleeding rates (GENA-21b and GENA-01) - all bleedings	PROPH, PROPH-PP	X	X*
14.2.10J	T	Prophylactic treatment phase II: Individual annualized total bleeding rates (GENA-21b and GENA-01) - all bleedings – Japanese Subgroup Analysis	J/NJ	X	-
14.2.11	T	Prophylactic treatment phase II: Individual annualized total bleeding rates (GENA-21b and GENA-01) - by type of bleeding	PROPH, PROPH-PP	X	X*
14.2.11J	T	Prophylactic treatment phase II: Individual annualized total bleeding rates (GENA-21b and GENA-01) - by type of bleeding – Japanese Subgroup Analysis	J/NJ	X	-
14.2.12.1	T	Prophylactic treatment phase II: Individual annualized total bleeding rates) - by prophylactic treatment scheme (<=- 2 times per week vs. > 2 times per week)	PROPH, PROPH-PP	X	X*
14.2.12.2	T	Prophylactic treatment phase II: Individual annualized total bleeding rates - by dosing intervals	PROPH, PROPH-PP	X	X*
14.2.12.3	T	Prophylactic treatment phase II: Individual annualized total bleeding rates - first 4 months of Prophylactic Treatment Phase II	PROPH, PROPH-PP	X	-
14.2.12.4	T	Prophylactic treatment phase II: Individual annualized total bleeding rates - last 2 months of Prophylactic Treatment Phase II	PROPH, PROPH-PP	X	-
14.2.12.5	T	Prophylactic treatment phase II: Individual annualized total bleeding rates - first 4 months of Prophylactic Treatment Phase II - by prophylactic treatment scheme (<= twice per week vs. > twice per week)	PROPH, PROPH-PP	X	-
14.2.12.6	T	Prophylactic treatment phase II: Individual annualized total bleeding rates - last 2 months of Prophylactic Treatment Phase II - by prophylactic treatment scheme (<= twice per week vs. > twice per week)	PROPH, PROPH-PP	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.2.13.1	T	Prophylactic treatment phase II: Individual annualized total bleeding rates (GENA-21b and GENA-01) - by severity of bleeding events	PROPH, PROPH-PP	X	X*
14.2.13.1J	T	Prophylactic treatment phase II: Individual annualized total bleeding rates (GENA-21b and GENA-01) - by severity of bleeding events - – Japanese Subgroup Analysis	J/NJ	X	-
14.2.13.2	T	Prophylactic treatment phase II: Individual annualized total bleeding rates (GENA-21b and GENA-01) - by joint / non-joint bleedings	PROPH, PROPH-PP	X	X*
14.2.13.2J	T	Prophylactic treatment phase II: Individual annualized total bleeding rates (GENA-21b and GENA-01) - by joint / non-joint bleedings - – Japanese Subgroup Analysis	J/NJ	X	-
14.2.14.1	T	Prophylactic treatment phase II: Poisson test primary endpoint: Test on mean annualized total bleeding rate compared to 50% of observed annualized total bleeding rate in the GENA-01 study	PROPH, PROPH-PP	X	-
14.2.14.1J	T	Prophylactic treatment phase II: Poisson test primary endpoint: Test on mean annualized total bleeding rate compared to 50% of observed annualized total bleeding rate in the GENA-01 study – Japanese Subgroup Analysis	J/NJ	X	-
14.2.14.2	T	Prophylactic treatment phase I: Poisson test: Test on mean annualized total bleeding rate compared to 50% of observed annualized total bleeding rate in the GENA-01 study	PROPH, PROPH-PP	X	-
14.2.14.2J	T	Prophylactic treatment phase I: Poisson test: Test on mean annualized total bleeding rate compared to 50% of observed annualized total bleeding rate in the GENA-01 study – Japanese Subgroup Analysis	J/NJ	X	-
14.2.15	T	Prophylactic treatment phase II: Poisson test 1st secondary endpoint: Test on mean annualized bleeding rate compared to 50% of observed annualized total bleeding rate in the GENA-01 study -by type of bleeding (spontaneous, traumatic, other)	PROPH, PROPH-PP	X	-
14.2.16	T	Prophylactic treatment phase II: Poisson test 2nd secondary endpoint: Test on mean annualized total bleeding rate in patients with 2x/week prophylaxis or less compared to 50% of observed annualized total bleeding rate in the GENA-01 study	PROPH, PROPH-PP (Subgroups)	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.2.17.1. 1	T	Prophylactic treatment phase II: Annualized Bleeding Rate and monthly bleeding rate estimated from individual annualized bleeding rate with Poisson regression and negative binomial regression model, including 95% confidence intervals (All bleedings, spontaneous, traumatic)	PROPH, PROPH-PP	X	X*
14.2.17.1J	T	Prophylactic treatment phase II: Annualized Bleeding Rate and monthly bleeding rate estimated from individual annualized bleeding rate with Poisson regression and negative binomial regression model, including 95% confidence intervals (All bleedings, spontaneous, traumatic) – Japanese Subgroup Analysis	J/NJ	X	-
14.2.17.1. 2	T	Prophylactic treatment phase I: Annualized Bleeding Rate and monthly bleeding rate estimated from individual annualized bleeding rate with Poisson regression and negative binomial regression model, including 95% confidence intervals (All bleedings, spontaneous, traumatic)	PROPH, PROPH-PP	X	-
14.2.17.1. 2J	T	Prophylactic treatment phase I: Annualized Bleeding Rate and monthly bleeding rate estimated from individual annualized bleeding rate with Poisson regression and negative binomial regression model, including 95% confidence intervals (All bleedings, spontaneous, traumatic) – Japanese Subgroup Analysis	J/NJ	X	-
14.2.17.2	T	Prophylactic treatment phase II: Annualized Bleeding Rate and monthly bleeding rate estimated from individual annualized bleeding rate with Poisson regression and negative binomial regression model, including 95% confidence intervals (All bleedings, prophylactic treatment schemes with <= 2 times per week and > 2 times per week)	PROPH, PROPH-PP	X	X
14.2.18.1	T	Comparison of Annualized Bleeding Rate between GENA-21b, Prophylactic Treatment Phase II and GENA-01. Bleeding rates estimated from individual annualized bleeding rates with negative binomial regression model, including 95% confidence intervals for the rate ratio between studies (All bleedings, spontaneous, traumatic)	PROPH, PROPH-PP	X	-
14.2.18.1. 2J	T	Comparison of Annualized Bleeding Rate between GENA-21b, Prophylactic Treatment Phase II and GENA-01. Bleeding rates estimated from individual annualized bleeding rates with negative binomial regression model, including 95% confidence intervals for the rate ratio between studies (All bleedings, spontaneous, traumatic) – Japanese Subgroup Analysis	J/NJ	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.2.18.2	T	Comparison of Annualized Bleeding Rate between GENA-21b, Prophylactic Treatment Phase II and GENA-01. Bleeding rates estimated from individual annualized bleeding rates with Poisson regression model, including 95% confidence intervals for the rate ratio between studies (All bleedings, spontaneous, traumatic)	PROPH, PROPH-PP	X	-
14.2.18.2. 2J	T	Comparison of Annualized Bleeding Rate between GENA-21b, Prophylactic Treatment Phase II and GENA-01. Bleeding rates estimated from individual annualized bleeding rates with Poisson regression model, including 95% confidence intervals for the rate ratio between studies (All bleedings, spontaneous, traumatic) – Japanese Subgroup Analysis	J/NJ	X	-
14.2.19.1	T	Within-subject comparison of Annualized Bleeding Rate between Prophylactic Treatment Phase II and Prophylactic Treatment Phase I: Distribution of intra-individual differences (All bleedings, spontaneous, traumatic)	PROPHc, PROPHc-PP	X	-
14.2.19.2	T	Within-subject comparison of Annualized Bleeding Rate between Prophylactic Treatment Phase II and Prophylactic Treatment Phase I: Mantel-Haenszel type estimate for the rate ratio with confidence intervals (All bleedings, spontaneous, traumatic)	PROPHc, PROPHc-PP	X	-
		Pharmakokinetics			
14.2.20	T	Doses administered for PK assessments (*Doses in IU and in IU/kg)*	ITT, PK, PK-PP, PROPH	X	-
14.2.21.1	F	Mean (+/- SD) FVIII:C levels (IU/mL) for one-stage assay and chromogenic assay – PKPP	PKPP	X	-
14.2.21.1J	F	Mean (+/- SD) FVIII:C levels (IU/mL) for one-stage assay and chromogenic assay – PKPP – Japanese Subgroup Analysis	J/NJ	X	-
14.2.21.2	F	Mean (+/- SD) FVIII:C levels (IU/mL) for one-stage assay and chromogenic assay - standardized to 60 IU/kg – PKPP	PKPP	X	-
14.2.21.2J	F	Mean (+/- SD) FVIII:C levels (IU/mL) for one-stage assay and chromogenic assay - standardized to 60 IU/kg – PKPP – Japanese Subgroup Analysis	J/NJ	X	-
14.2.21.3	F	Mean (+/- SD) FVIII:C levels (IU/mL) for one-stage assay - standardized to 60 IU/kg - log-linear scale - PKPP	PKPP	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.2.21.3J	F	Mean (+/- SD) FVIII:C levels (IU/mL) for one-stage assay - standardized to 60 IU/kg - log-linear scale – PKPP – Japanese Subgroup Analysis	J/NJ	X	-
14.2.21.4	F	Mean (+/- SD) FVIII:C levels (IU/mL) for chromogenic assay - standardized to 60 IU/kg - log-linear scale - PKPP	PKPP	X	-
14.2.21.4J	F	Mean (+/- SD) FVIII:C levels (IU/mL) for chromogenic assay - standardized to 60 IU/kg - log-linear scale – PKPP – Japanese Subgroup Analysis	J/NJ	X	-
14.2.22	T	Statistics on FVIII concentrations (IU/mL), nominal time points	ITT, PK-PP, PK, PROPH,	X	-
14.2.22J	T	Statistics on FVIII concentrations (IU/mL), nominal time points – Japanese Subgroup Analysis	J/NJ	X	-
14.2.23.1	T	Statistics on FVIII concentrations (IU/mL) trough levels for time points during Prophylactic Treatment Phase II *(inc. also FVIII levels measured before, during and after surgery)*	PROPH, PROPH-PP	X	-
14.2.23.2	T	Statistics on FVIII concentration (IU/mL) trough levels measured after wash-out of approximately one prophylactic treatment interval for time points during Prophylactic Treatment Phase II	PROPH, PROPH-PP	X	-
14.2.24	T	Statistics on AUC and AUCnorm of Human-cl rhFVIII (initial PK) for both assays	ITT, PK-PP, PK, PROPH	X	-
14.2.24J	T	Statistics on AUC and AUCnorm of Human-cl rhFVIII (initial PK) for both assays – Japanese Subgroup Analysis	J/NJ	X	-
14.2.24.1	T	Statistics on AUC and AUCnorm of Human-cl rhFVIII for one-stage assay, PK model communicated to investigators as basis for dosing	ITT, PK-PP, PK, PROPH	X	-
14.2.24.1J	T	Statistics on AUC and AUCnorm of Human-cl rhFVIII for one-stage assay, PK model communicated to investigators as basis for dosing – Japanese Subgroup Analysis	J/NJ	X	-
14.2.25	T	Statistics on Cmax, Cmaxnorm and recovery of FVIII:C (IU/mL) after injection of Human-cl rh-FVIII (initial PK) based on the actual potency, both assays	ITT, PK-PP, PK, PROPH	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.2.25J	T	Statistics on Cmax, Cmaxnorm and recovery of FVIII:C (IU/mL) after injection of Human-cl rh-FVIII (initial PK) based on the actual potency, both assays – Japanese Subgroup Analysis	J/NJ	X	-
14.2.26	T	Statistics on Tmax (h) after injection of Human-cl rhFVIII (initial PK) both assays	ITT, PK-PP, PK, PROPH	X	-
14.2.26J	T	Statistics on Tmax (h) after injection of Human-cl rhFVIII (initial PK) both assays – Japanese Subgroup Analysis	J/NJ	X	-
14.2.27	T	Statistics on T1/2 and MRT after injection of Human-cl rhFVIII (initial PK) based on the actual potency, both assays	ITT, PK-PP, PK, PROPH	X	-
14.2.27J	T	Statistics on T1/2 and MRT after injection of Human-cl rhFVIII (initial PK) based on the actual potency, both assays – Japanese Subgroup Analysis	J/NJ	X	-
14.2.27.1	T	Statistics on Half-lives and MRT after injection of Human-cl rhFVIII based on the actual potency, one-stage assay - PK model communicated to investigators as basis for dosing	ITT, PK-PP, PK, PROPH	X	-
14.2.27.1J	T	Statistics on Half-lives and MRT after injection of Human-cl rhFVIII based on the actual potency, one-stage assay - PK model communicated to investigators as basis for dosing – Japanese Subgroup Analysis	J/NJ	X	-
14.2.27.2	T	Statistics on terminal half-life (both assays) by ABO blood type (Type 0 vs. Non-0)	ITT, PK-PP, PK, PROPH	X	-
14.2.28	T	Statistics on Cl and Vss after injection of Human-cl rhFVIII (initial PK) based on the actual potency, both assays	ITT, PK-PP, PK, PROPH	X	-
14.2.28J	T	Statistics on Cl and Vss after injection of Human-cl rhFVIII (initial PK) based on the actual potency, both assays – Japanese Subgroup Analysis	J/NJ	X	-
14.2.28.1	T	Statistics on Cl and Vss after injection of Human-cl rhFVIII based on the actual potency, one-stage assay - PK model communicated to investigators as basis for dosing	ITT, PK-PP, PK, PROPH	X	-
14.2.28.1J	T	Statistics on Cl and Vss after injection of Human-cl rhFVIII based on the actual potency, one-stage assay - PK model communicated to investigators as basis for dosing – Japanese Subgroup Analysis	J/NJ	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.2.29	T	Frequency distribution of Tmax (h) after injection of Human-cl rhFVIII , both assays	ITT, PK-PP, PK, PROPH	X	-
14.2.29J	T	Frequency distribution of Tmax (h) after injection of Human-cl rhFVIII , both assays – Japanese Subgroup Analysis	J/NJ	X	-
		vWFAg			
14.2.30.1	T	Statistics on vWFAg before initial PK infusion	PK, PK-PP	X	-
14.2.30.1J	T	Statistics on vWFAg before initial PK infusion – Japanese Subgroup Analysis	J/NJ	X	-
14.2.30.2	T	Statistics on vWFAg by ABO blood types	ITT, PK, PK-PP, PROPH	X	-
14.2.31.1	T	Statistical-Output: Correlation of vWF antigen concentration at screening and (terminal) half-life, one-stage assay *Pearson and Spearman correlation*	PK, PK-PP	X	-
14.2.31.2	T	Statistical-Output: Correlation of vWF antigen concentration at screening and (terminal) half-life, chromogenic assay *Pearson and Spearman correlation*	PK, PK-PP	X	-
		Bleedings			
14.2.32	T	Number and frequency of bleedings per subject (in both phases of study)	ITT, PP, PROPH, PROPH-PP	X	X
14.2.33	T	Frequency of bleedings per site of bleeding and in total	BLEED, BLEED-PP	X	X
14.2.34	T	Frequency of bleedings per type of bleeding (spontaneous, traumatic, post-operative, other) and in total	BLEED, BLEED-PP	X	X
14.2.35	T	Severity of bleedings by site of bleeding (frequency counts)	BLEED, BLEED-PP	X	X

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.2.36	T	Treatment duration for bleeding episodes per severity and in total	BLEED, BLEED-PP	X	X
14.2.37	T	Personal efficacy assessment (final outcome) of treatment of bleeding episode - Four-point scale	BLEED, BLEED-PP	X	X
14.2.37J	T	Personal efficacy assessment (final outcome) of treatment of bleeding episode - Four-point scale – Japanese Subgroup Analysis	BLEED, BLEED-PP in J/NJ	X	-
14.2.38	T	Success rate and 95% confidence intervals regarding personal efficacy assessment (final outcome) of treatment of bleeding episode	BLEED, BLEED-PP	X	-
14.2.38J	T	Success rate and 95% confidence intervals regarding personal efficacy assessement (final outcome) of treatment of bleeding episode – Japanese Subgroup Analysis	BLEED, BLEED-PP in J/NJ	X	-
14.2.39	T	Predicted probabilities of success and 95% CI using a Generalized Estimation Equation with intra-subject covariance structure. Personal efficacy assessment (final outcome) of treatment of bleeding	BLEED, BLEED-PP	X	-
14.2.39J	T	Predicted probabilities of success and 95% CI using a Generalized Estimation Equation with intra-subject covariance structure. Personal efficacy assessment (final outcome) of treatment of bleeding– Japanese Subgroup Analysis	BLEED, BLEED-PP PP in J/NJ	X	-
14.2.40	T	Statistics on the number of exposure days to Human-cl rhFVIII and injections administered	BLEED, BLEED-PP	X	X
14.2.41	T	Statistics on dose (IU and IU/kg) and number of infusions per bleeding episode per bleeding site and in total	BLEED, BLEED-PP	X	X
14.2.41J	T	Statistics on dose (IU and IU/kg) and number of infusions per bleeding episode per bleeding site and in total – Japanese Subgroup Analysis	J/NJ	X	-
14.2.42	T	Statistics on dose (IU and IU/kg) of Human-cl rhFVIII per infusion per BE per severity of BE and in total	BLEED, BLEED-PP	X	X
14.2.43	T	Statistics on dose (IU and IU/kg) of Human-cl rhFVIII per infusion per bleeding site and in total	BLEED, BLEED-PP	X	X

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.2.44	T	Statistics on dose (IU and IU/kg) of Human-cl rhFVIII per exposure day per bleeding site and in total	BLEED, BLEED-PP	X	X
14.2.45	T	Statistics on dose (IU and IU/kg) of Human-cl rhFVIII per subject per week, per month and per year for bleeding events	ITT, PP-population	X	X
14.2.45J	T	Statistics on dose (IU and IU/kg) of Human-cl rhFVIII per subject per week, per month and per year for bleeding events – Japanese Subgroup Analysis	J/NJ	X	-
14.2.46	T	Statistics on dose (IU and IU/kg) per bleeding episode by severity and efficacy	BLEED, BLEED-PP	X	X
14.2.47	T	Frequency of bleeding episodes per subject in BLEED populations	PROPH, PROPH-PP	X	X
14.2.48	T	Frequency of all bleeding episodes after first study drug administration - SAF population (inc. Number of untreated bleedings)	SAF	X	X
14.2.49	T	Number of treatment days per bleeding	BLEED, BLEED-PP	X	X
		Surgery			
14.2.50	T	Subjects included in surgery analysis (minor, major, total)	ITT, PP	X	X
14.2.51	T	Number of surgical procedures (minor, major, total)	SURG	X	X
14.2.52	T	Surgery characteristics	SURG, SURG-PP	X	X
14.2.53	T	Efficacy evaluation of the use of Human-cl rhFVIII in surgical procedures	SURG, SURG-PP	X	X
14.2.54	T	Frequency of use of concomitant medications by ATC class during surgery	SURG, SURG-PP	X	X
14.2.55	T	Statistics on number of infusions and exposure days for surgeries per severity and in total	SURG, SURG-PP	X	X

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.2.56	T	Statistics on total dose of Human-cl rhFVIII (IU, IU/kg, IU/kg and ED, IU per infusion, IU/kg and infusion) for surgeries per severity and in total	SURG, SURG-PP	X	X
14.2.57	T	Statistics on pre-operative loading dose before surgery (IU and IU/kg)	SURG, SURG-PP	X	X
14.2.58	T	Statistics on infusions administered during the surgery (maintenance doses)	SURG, SURG-PP	X	X
14.2.59	T	Statistics on infusions administered after end of the surgery	SURG, SURG-PP	X	X
14.2.60	T	Statistics on expected (average and maximum), actual blood loss and difference between actual and expected blood loss	SURG, SURG-PP	X	X
14.2.61	T	Statistics on expected and actual duration of the surgical procedure and difference between actual and expected duration	SURG, SURG-PP	X	X
		Safety			
14.3.1.1	T	Extent of exposure (nominal doses of Human-cl rhFVIII)	SAF	X	X
14.3.1.1J	T	Extent of exposure (nominal doses of Human-cl rhFVIII) – Japanese Subgroup Analysis	J/NJ	X	-
14.3.1.2	T	Summary of adverse events	SAF	X	X
14.3.1.2J	T	Summary of adverse events – Japanese Subgroup Analysis	J/NJ	X	-
14.3.1.3	T	Treatment-emergent adverse events by preferred term per subject (descending frequency)	SAF	X	X
14.3.1.3J	T	Treatment-emergent adverse events by preferred term per subject (descending frequency) – Japanese Subgroup Analysis	J/NJ	X	-
14.3.1.4	T	Treatment-emergent adverse events by preferred term per infusion (descending frequency)	SAF	X	X
14.3.1.4J	T	Treatment-emergent adverse events by preferred term per infusion (descending frequency) – Japanese Subgroup Analysis	J/NJ	X	-
14.3.1.5	T	Treatment-emergent adverse events by system organ class and preferred term	SAF	X	X

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.3.1.5J	T	Treatment-emergent adverse events by system organ class and preferred term – Japanese Subgroup Analysis	J/NJ	X	-
14.3.1.6	T	Treatment-emergent possibly/probably related adverse events by system organ class and preferred term	SAF, INF	X	X
14.3.1.7	T	Treatment-emergent adverse events temporally related (within 24 hours after end of infusion) by system organ class and preferred term	SAF, INF	X	X
14.3.1.8	T	Severity of treatment-emergent adverse events by system organ class and preferred term (SAF)	SAF	X	X
14.3.1.9	T	Severity of treatment-emergent adverse events by system organ class and preferred term (INF)	INF	X	X
14.3.1.10	T	Summary of adverse events – Prophylactic Treatment Phase I (without AEs after surgical interventions)	SAF, INF	X	-
14.3.1.10J	T	Summary of adverse events – Prophylactic Treatment Phase I (without AEs after surgical interventions) – Japanese Subgroup Analysis	J/NJ in SAF, INF	X	-
14.3.1.11	T	Treatment-emergent adverse events by system organ class and preferred term - Prophylactic Treatment Phase I (without AEs after surgical interventions)	SAF, INF	X	-
14.3.1.11J	T	Treatment-emergent adverse events by system organ class and preferred term - Prophylactic Treatment Phase I (without AEs after surgical interventions) – Japanese Subgroup Analysis	J/NJ in SAF, INF	X	-
14.3.1.12	T	Summary of adverse events – Prophylactic Treatment Phase II (without AEs after surgical interventions)	SAF, INF	X	-
14.3.1.12J	T	Summary of adverse events – Prophylactic Treatment Phase II (without AEs after surgical interventions) – Japanese Subgroup Analysis	J/NJ in SAF, INF	X	-
14.3.1.13	T	Treatment-emergent adverse events by system organ class and preferred term - Prophylactic Treatment Phase II (without AEs after surgical interventions)	SAF, INF	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.3.1.13J	T	Treatment-emergent adverse events by system organ class and preferred term - Prophylactic Treatment Phase II (without AEs after surgical interventions) – Japanese Subgroup Analysis – Japanese Subgroup Analysis	J/NJ in SAF, INF	X	-
14.3.1.14	T	Summary of adverse events – during and after surgical interventions (up to last day in hospital (=day of surgery for ambulant surgeries))	SAF, INF	X	X
14.3.1.15	T	Treatment-emergent adverse events by system organ class and preferred term – during and after surgical interventions (up to last day in hospital (=day of surgery for ambulant surgeries)	SAF, INF	X	X
14.3.1.16	T	Summary of adverse events – by age-groups 18-65 years, > 65 years)	SAF, INF	X	X
14.3.2.1	T	Treatment-emergent serious adverse events by system organ class and preferred term	SAF, INF	X	X
14.3.2.2	L	Serious adverse events	SAF	X	X
14.3.2.3	L	Deaths	SAF	X	X
14.3.2.4	L	Adverse events leading to discontinuation of study medication or death	SAF	X	X
14.3.4.1.1	L	Abnormal laboratory (Hematology)	SAF	X	-
14.3.4.1.2	L	Abnormal laboratory (Biochemistry)	SAF	X	-
14.3.4.2.1	T	Hematology: Summary statistics for each lab parameter and time point (excluding surgery)	SAF	X	-
14.3.4.2.2	T	Clinical Chemistry: Summary statistics for each lab parameter and time point (excluding surgery)	SAF	X	-
14.3.4.2.3	T	Hematology: Summary statistics for each lab parameter before and after surgery	SAF	X	-
14.3.4.2.4	T	Clinical Chemistry: Summary statistics for each lab parameter before and after surgery	SAF	X	-
14.3.4.3.1	T	Vital Signs: Summary statistics on all vital sign determinations per time point (excluding surgery) and change from baseline before PK	SAF	X	-
14.3.4.3.2	T	Vital Signs: Summary statistics on all vital sign determinations per time point before, during and after surgery including changes from before surgery	SAF	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
14.3.4.3.3	T	Physical Examination shift table on the evaluations of each category included in the physical examination (baseline vs. month 6 visit)	SAF	X	-
14.3.4.3.3 E	T	Physical Examination shift table on the evaluations of each category included in the physical examination (Completion visit main study/ screening extension period vs. Completion visit extension period)	SAF_E	-	X
16.2		***Patient Data Listings (section 16.2 of the CSR)*** *Listings will generally be sorted by patient number* X* in Column “Japan. Sub-Study Extension Phase”: “Prophylactic Treatment Phase I”, “Prophylactic Treatment Phase II”, “both Prophylactic Treatment Phases”, “Prophylactic Treatment Phases I and II” to be replaced by “Japanese Sub-Study Extension Phase”			
16.2.1.1	L	Prematurely discontinued subjects - All enrolled subjects	SAF	X	X
16.2.1.2.1	L	Study completion - All enrolled subjects	SAF	X	X
16.2.1.2.2	L	Study completion - Completion of each phase of the study - All enrolled subjects	SAF	X	-
16.2.2.1	L	Major protocol deviations - All enrolled subjects	SAF	X	X
16.2.2.2	L	Minor protocol deviations and data issues (derived from database) - All enrolled subjects	SAF	X	X
16.2.3	L	Disposition of subjects with respect to analysis populations - All screened subjects	SAF	X	X
16.2.4.1	L	Subject demographics - All enrolled subjects	SAF	X	X
16.2.4.2	L	Medical history	SAF	X	X
16.2.4.3.1	L	Background data (Tables 14.1.5 – 14.1.8, 14.1.10, viral markers and CD4 count at screening) - All enrolled subjects	SAF	X	X
16.2.4.3.2	L	Target joints of Bleedings (Tables 14.1.14, target joints) - All enrolled subjects	SAF	X	-
16.2.4.4	L	Subject history: Haemophilia joint health score	SAF	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
16.2.4.5.1.1	L	Prior and concomitant medication – except for previous FVIII treatments of hemophilia A	SAF	X	X
16.2.4.5.1.2	L	Relevant concomitant medication in ATC class 'Blood and Blood Forming Organs'	SAF	X	X
16.2.4.5.2.1	L	Previous FVIII treatments of hemophilia A (During the last 6 months before screening)	SAF	X	-
16.2.4.5.2.2	L	Amounts of FVIII treatments for hemophilia A (During the last 6 months before screening)	SAF	X	-
16.2.4.5.3	L	Co-medication used in the treatment of bleeding episodes	BLEED	X	X
16.2.4.5.4	L	Concomitant medication during surgery	SURG	X	X
16.2.4.5.5	L	Relevant concomitant medication in ATC class 'Blood and Blood Forming Organs' during hospitalization for surgery	SURG	X	X
16.2.5.1	L	Human-cl rhFVIII doses during study including reason for treatment *(inc. marker for PROPH phase I or II)*	SAF	X	X
16.2.5.2	L	Number of infusions and Human-cl rhFVIII consumption per exposure day	SAF	X	X
16.2.5.3	L	Subject exposure (duration of treatment with Human-cl rhFVIII, exposure days, number of infusions)	SAF	X	X
16.2.5.4	L	Doses of Human-cl rhFVIII for PK	All	X	-
16.2.5.4.1	L	Batches of Human-cl rhFVIII used in the study and their potencies	All	X	X
16.2.5.5	L	FVIII concentrations (IU/mL) per assay during PK profile, trough level determination and surgeries	All	X	-
16.2.5.5.1	L	FVIII concentrations (IU/mL) per assay: Trough levels reported from central lab with relating dosing information	All	X	X
16.2.5.6.1	L	PK parameters of Human-cl rhFVIII (both assays) - Parameters for both one and two compartment models -	PK	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
16.2.5.6.2	L	PK parameters of *Human-cl rhFVIII* (both assays) - Additional PK parameters	PK	X	-
16.2.5.6.3	L	PK parameters of Human-cl rhFVIII (one-stage assay): PK model on which actual dose recommendation to the investigator was based	PK	X	-
16.2.5.6.4	L	PK parameters of Human-cl rhFVIII (one-stage assay): PK model on which actual dose recommendation to the investigator was based - Additional parameters	PK	X	-
16.2.5.7	L	Cmax, Cmaxnorm, tmax and recovery of FVIII:C for Human-cl rhFVIII (both assays, nominal and actual potencies)	PK	X	-
16.2.5.7.1	L	Cmax, Cmaxnorm, tmax and recovery of FVIII:C for Human-cl rhFVIII (one-stage assay, nominal and actual potencies) : Results communicated to investigators as basis for dosing	PK	X	-
16.2.5.8	L	Human-cl rhFVIII injections for prophylactic treatment during study *(inc. marker for prophylactic treatment phase)*	SAF	X	X
16.2.5.9	L	Exposure days and Human-cl rhFVIII consumption for prophylactic treatment *(inc. marker for prophylactic treatment phase)*	SAF	X	X
16.2.5.10. 1	L	Listing of Prophylactic treatment schedules per Visit - Prophylactic Treatment Phases I and II	SAF	X	X*
16.2.5.10. 2	L	Consumption of Human-cl rhFVIII for prophylactic treatment per week, per month, per year, per prophylactic treatment episode, exposure day and in total – Prophylactic treatment phase I	SAF	X	-
16.2.5.10. 3.1	L	Consumption of Human-cl rhFVIII for prophylactic treatment per week, per month, per year, per prophylactic treatment episode, exposure day and in total – Prophylactic treatment phase II	PROPH, PROPH.PP	X	-
16.2.5.10. 3.2	L	Consumption of Human-cl rhFVIII for prophylactic treatment per week, per month, per year, per prophylactic treatment episode, exposure day and in total – First 4 months of Prophylactic treatment phase II	PROPH, PROPH.PP	X	-
16.2.5.10. 3.3	L	Consumption of Human-cl rhFVIII for prophylactic treatment per week, per month, per year, per prophylactic treatment episode, exposure day and in total – Last 2 months of Prophylactic treatment phase II	PROPH, PROPH.PP	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
16.2.5.10. 4	L	Consumption of Human-cl rhFVIII for prophylactic treatment per week, per month, per year, per prophylactic treatment episode, exposure day and in total – both Prophylactic Treatment Phases	ITT, PP, PROPH, PROPH-PP	X	X*
16.2.5.11	L	Personalized prophylactic treatment scheme for Prophylactic Treatment Phase II: Calculated schemes, actual starting scheme, last scheme applied	PROPH	X	X*
16.2.5.12	L	Changes in prophylactic dose schemes	PROPH	X	X
16.2.5.13	L	Dose of Human-cl rhFVIII for surgical reasons	SURG	X	X
16.2.5.14	L	Pre-, intra- and post-operative FVIII:C plasma levels	SURG	X	X
16.2.6.1.1. 1.1-7	L	Number of bleedings, rate per month, annualized bleeding rate, first and last prophylactic scheme (Phase II),, characteristics of bleeding - Prophylactic Treatment Phase II and GENA-01 study Separate listings for all, spontaneous, traumatic, minor, at least moderate, joint, non-joint bleedings	PROPH	X	-
16.2.6.1.1. 2.1-7	L	Number of bleedings, Number of bleedings, rate per month, annualized bleeding rate, first and last prophylactic scheme (Phase II), characteristics of bleeding - First 4 months of prophylactic Treatment Phase II Separate listings for all, spontaneous, traumatic, minor, at least moderate, joint, non-joint bleedings	PROPH	X	-
16.2.6.1.1. 3.1-7	L	Number of bleedings, rate per month, annualized bleeding rate, first and last prophylactic scheme (Phase II), characteristics of bleeding - Last 2 months of prophylactic Treatment Phase II Separate listings for all, spontaneous, traumatic, minor, at least moderate, joint, non-joint bleedings	PROPH	X	-
16.2.6.1.1 4.1-7	L	Number of bleeding episodes, rate per month, annualized bleeding rate, characteristics of bleeding – Prophylactic Treatment Phase I Separate listings for all, spontaneous, traumatic, minor, at least moderate, joint, non-joint bleedings	SAF	X	X*

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
16.2.6.1.2	L	Intra-individual comparison of bleeding rates between Prophylactic Treatment Phase I and II: Characteristics of bleeding (All, spontaneous, traumatic), Number of bleeding episodes (Phase I and Phase II), observation time (Phase I and II), annualized bleeding rate (Phase I and II), difference in ABR, ABR ratio	PROPH	X	-
16.2.6.2	L	von Willebrand factor antigen (vWFAg) data (inc. changes from baseline)	PK	X	-
16.2.6.3	L	Bleeding episodes during study	BLEED	X	X
16.2.6.4	L	Bleeding episodes, doses and changes in dose per infusion for each bleeding episode during study	BLEED	X	X
16.2.6.5	L	Bleeding episodes by site of bleeding, efficacy assessments, doses and changes in dose per BE and per infusion by type of BE	BLEED	X	X
16.2.6.6	L	Individual doses and consumption of Human-cl rhFVIII for bleedings in BLEED population	SAF	X	X
16.2.6.7.1.1	L	Surgeries: Description and outcome of surgical procedures	SURG	X	X
16.2.6.7.1.2	L	Surgeries: Description and outcome of surgical procedures – Hospitalization	SURG	X	X
16.2.6.7.2	L	Surgeries: Description of wound hematoma and whether it needed surgical evacuation yes/no	SURG	X	X
16.2.6.7.3	L	Surgeries: Description and assignment to SURG/SURG-PP populations including reasons for exclusion	SURG	X	X
16.2.6.7.4	L	Surgeries: Blood loss (planned and actual), duration of surgery (planned and actual)	SURG	X	X
16.2.7.1	L	Adverse events	SAF	X	X
16.2.7.2	L	Possibly/probably related adverse events	SAF	X	X
16.2.7.3	L	Non-treatment emergent adverse events	SAF	X	X
16.2.8.1.1	L	Laboratory assessments (Hematology)	SAF	X	X

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
16.2.8.1.2	L	Laboratory assessments (Biochemistry)	SAF	X	X
16.2.8.2	L	FVIII:C, inhibitor and anti-rhFVIII antibody determinations	SAF	X	X
16.2.8.3	L	Vital signs	SAF	X	X
16.2.8.41	L	Physical examination	SAF	X	X
16.2.8.4.2	L	Abnormal findings of physical examination	SAF	X	X
16.2.9	L	Additional comments provided in the CRF	SAF	X	X
		SAS Output of special statistical model analyses			
16.2.10.1.1	L	Statistical output of PROC GENMOD: Prophylactic treatment phase II: Negative binomial regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - All bleedings	PROPH, PROPH-PP	X	-
16.2.10.1.1J	L	Statistical output of PROC GENMOD: Prophylactic treatment phase II: Negative binomial regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - All bleedings– Japanese Subgroup Analysis	J/NJ	X	-
16.2.10.1.2	L	Statistical output of PROC GENMOD: Prophylactic treatment phase II: Negative binomial regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - All bleedings	PROPH, PROPH-PP	X	-
16.2.10.1.2J	L	Statistical output of PROC GENMOD: Prophylactic treatment phase I: Negative binomial regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - All bleedings – Japanese Subgroup Analysis	J/NJ	X	-
16.2.10.2	L	Statistical output of PROC GENMOD: : Prophylactic treatment phase II: Negative binomial regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - Spontaneous bleedings -	PROPH, PROPH-PP	X	-
16.2.10.3	L	Statistical output of PROC GENMOD: : Prophylactic treatment phase II: Negative binomial regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - Traumatic bleedings	PROPH, PROPH-PP	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
16.2.10.4. 1	L	Statistical output of PROC GENMOD: Prophylactic treatment phase II: Poisson regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - All bleedings	PROPH, PROPH-PP	X	-
16.2.10.4. 1J	L	Statistical output of PROC GENMOD: Prophylactic treatment phase II: Poisson regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - All bleedings– Japanese Subgroup Analysis	J/NJ	X	-
16.2.10.4. 2	L	Statistical output of PROC GENMOD: Prophylactic treatment phase II: Poisson regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - All bleedings	PROPH, PROPH-PP	X	-
16.2.10.4. 2J	L	Statistical output of PROC GENMOD: Prophylactic treatment phase II: Poisson regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - All bleedings– Japanese Subgroup Analysis	J/NJ	X	-
16.2.10.5	L	Statistical output of PROC GENMOD: : Prophylactic treatment phase II: Poisson regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - Spontaneous bleedings -	PROPH, PROPH-PP	X	-
16.2.10.6	L	Statistical output of PROC GENMOD: : Prophylactic treatment phase II: Poisson regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - Traumatic bleedings	PROPH, PROPH-PP	X	-
16.2.10.7	L	Statistical output of PROC GENMOD: Prophylactic treatment phase II: Negative binomial regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - Life-threatening bleedings -	PROPH, PROPH-PP	X	-
16.2.10.8	L	Statistical output of PROC GENMOD: Prophylactic treatment phase II: Negative binomial regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - Major bleedings -	PROPH, PROPH-PP	X	-
16.2.10.9	L	Statistical output of PROC GENMOD: Prophylactic treatment phase II: Poisson regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - Life-threatening bleedings -	PROPH, PROPH-PP	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
16.2.10.10	L	Statistical output of PROC GENMOD: Prophylactic treatment phase II: Poisson regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - Major bleedings -	PROPH, PROPH-PP	X	-
16.2.10.11	L	Statistical output of PROC GENMOD: : Prophylactic treatment phase II: Negative binomial regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable – Joint bleedings	PROPH, PROPH-PP	X	-
16.2.10.12	L	Statistical output of PROC GENMOD: : Prophylactic treatment phase II: Negative binomial regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable – Non-joint bleedings	PROPH, PROPH-PP	X	-
16.2.10.13	L	Statistical output of PROC GENMOD: Prophylactic treatment phase II: Negative binomial for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - Joint bleedings	PROPH, PROPH-PP	X	-
16.2.10.14	L	Statistical output of PROC GENMOD: : Prophylactic treatment phase II: Poisson regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - Non-joint bleedings	PROPH, PROPH-PP	X	-
16.2.10.15	L	Statistical output of PROC GENMOD: : Prophylactic treatment phase II: Negative binomial regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable – prophylactic treatment scheme with <= 2 times per week dosing	PROPH, PROPH-PP	X	-
16.2.10.16	L	Statistical output of PROC GENMOD: Prophylactic treatment phase II: Poisson regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - prophylactic treatment scheme with > 2 times per week dosing	PROPH, PROPH-PP	X	-
16.2.10.17 1	L	Statistical output of PROC GENMOD: : Prophylactic treatment phase II: Poisson regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - prophylactic treatment scheme with <= 2 times per week dosing	PROPH, PROPH-PP	X	-
16.2.10.18	L	Statistical output of PROC GENMOD: : Prophylactic treatment phase II: Poisson regression for frequency of BEs corrected for overdispersion with observed prophylactic treatment period as offset variable - prophylactic treatment scheme with > 2 times per week dosing	PROPH, PROPH-PP	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
16.2.11.1	L	Between study analysis GENA-21b and GENA-01: Statistical output of PROC GENMOD: Negative binomial regression model for frequency of BEs corrected for overdispersion with study as covariate and observed prophylactic treatment period as offset variable - All bleedings	PROPH, PROPH-PP	X	-
16.2.11.1J	L	Between study analysis GENA-21b and GENA-01: Statistical output of PROC GENMOD: Negative binomial regression model for frequency of BEs corrected for overdispersion with study as covariate and observed prophylactic treatment period as offset variable - All bleedings – Japanese Subgroup Analysis	PROPH, PROPH-PP	X	-
16.2.11.2	L	Between study analysis GENA-21b and GENA-01: Statistical output of PROC GENMOD: Negative binomial regression model for frequency of BEs corrected for overdispersion with study as covariate and observed prophylactic treatment period as offset variable - Spontaneous bleedings	PROPH, PROPH-PP	X	-
16.2.11.2J	L	Between study analysis GENA-21b and GENA-01: Statistical output of PROC GENMOD: Negative binomial regression model for frequency of BEs corrected for overdispersion with study as covariate and observed prophylactic treatment period as offset variable - Spontaneous bleedings – Japanese Subgroup Analysis	PROPH, PROPH-PP	X	-
16.2.11.3	L	Between study analysis GENA-21b and GENA-01: Statistical output of PROC GENMOD: Negative binomial regression model for frequency of BEs corrected for overdispersion with study as covariate and observed prophylactic treatment period as offset variable - Traumatic bleedings -	PROPH, PROPH-PP	X	-
16.2.11.3J	L	Between study analysis GENA-21b and GENA-01: Statistical output of PROC GENMOD: Negative binomial regression model for frequency of BEs corrected for overdispersion with study as covariate and observed prophylactic treatment period as offset variable - Traumatic bleedings -– Japanese Subgroup Analysis	PROPH, PROPH-PP	X	-
16.2.11.4	L	Between study analysis GENA-21b and GENA-01: Statistical output of PROC GENMOD: Poisson regression model for frequency of BEs corrected for overdispersion with study as covariate and observed prophylactic treatment period as offset variable - All bleedings	PROPH, PROPH-PP	X	-

No.	T/ L/ F	*Title*	Population	Main study	Japan.“Sub -Study Ext. Phase”
16.2.11.4J	L	Between study analysis GENA-21b and GENA-01: Statistical output of PROC GENMOD: Poisson regression model for frequency of BEs corrected for overdispersion with study as covariate and observed prophylactic treatment period as offset variable - All bleedings – Japanese Subgroup Analysis	PROPH, PROPH-PP	X	-
16.2.11.5	L	Between study analysis GENA-21b and GENA-01: Statistical output of PROC GENMOD: Poisson regression model for frequency of BEs corrected for overdispersion with study as covariate and observed prophylactic treatment period as offset variable - Spontaneous bleedings -	PROPH, PROPH-PP	X	-
16.2.11.5J	L	Between study analysis GENA-21b and GENA-01: Statistical output of PROC GENMOD: Poisson regression model for frequency of BEs corrected for overdispersion with study as covariate and observed prophylactic treatment period as offset variable - Spontaneous bleedings -– Japanese Subgroup Analysis	PROPH, PROPH-PP	X	-
16.2.11.6	L	Between study analysis GENA-21b and GENA-01: Statistical output of PROC GENMOD: Poisson regression model for frequency of BEs corrected for overdispersion with study as covariate and observed prophylactic treatment period as offset variable - Traumatic bleedings -	PROPH, PROPH-PP	X	-
16.2.11.6J	L	Between study analysis GENA-21b and GENA-01: Statistical output of PROC GENMOD: Poisson regression model for frequency of BEs corrected for overdispersion with study as covariate and observed prophylactic treatment period as offset variable - Traumatic bleedings -– Japanese Subgroup Analysis	PROPH, PROPH-PP	X	-
16.2.12.1	L	Statistical output of PROC GENMOD: General estimation equation for haemostatic success of treatment of bleedings with intra-subject covariance structure. Personal efficacy assessment (final outcome) of treatment of bleeding – Patients with any BE in BLEED population (Correlation matrix type: Exchangeable)	Patients with BE in BLEED	X	-
16.2.12.1J	L	Statistical output of PROC GENMOD: General estimation equation for haemostatic success of treatment of bleedings with intra-subject covariance structure. Personal efficacy assessment (final outcome) of treatment of bleeding – Patients with any BE in BLEED population (Correlation matrix type: Exchangeable) – Japanese Subgroup Analysis	Patients in J/NJ with BE in BLEED	X	-

No.	**T/ L/ F**	***Title***	**Population**	**Main study**	**Japan.“Sub -Study Ext. Phase”**
16.2.12.2	L	Statistical output of PROC GENMOD: General estimation equation for haemostatic success of treatment of bleedings with intra-subject covariance structure. Personal efficacy assessment (final outcome) of treatment of bleeding – Patients with any BE in BLEED-PP population (Correlation matrix type: Exchangeable)	Patients with BE in BLEED-PP	X	-
16.2.12.2J	L	Statistical output of PROC GENMOD: General estimation equation for haemostatic success of treatment of bleedings with intra-subject covariance structure. Personal efficacy assessment (final outcome) of treatment of bleeding – Patients with any BE in BLEED-PP population (Correlation matrix type: Exchangeable) – Japanese Subgroup Analysis	Patients in J/NJ Patients with BE in BLEED-PP	X	-

Appendices with detailed PK analyses (only main study)

App 1	A	Graphs and WinNonlin outputs for individual PK Analysis (sequential during study) - Human-cl rhFVIII – One-stage assay	PK	YES
App 2	A	Graphs and WinNonlin outputs for individual PK Analysis (final analysis) - Human-cl rhFVIII – One-stage assay	PK	NO
App 3	A	Graphs and WinNonlin outputs for individual PK Analysis (final analysis) - Human-cl rhFVIII - Chromogenic assay	PK	NO

TLGs for sequential PK during study (only main study):

Listing SeqPK 16.2.5.4	Doses of Human-cl rhFVIII for PK *(actual doses only for one stage assay)*
Listing SeqPK 16.2.5.5	FVIII concentrations (IU/mL) per assay during PK profile *(for one stage assay only)*
Listing SeqPK 16.2.5.6	PK parameters of Human-cl rhFVIII (one stage assay)
Listing SeqPK 16.2.5.7	Cmax, Cmaxnorm, tmax and recovery of FVIII:C for Human-cl rhFVIII ((one stage assay), nominal and actual potencies)
Listing SeqPK 16.2.5.11	Individually tailorized prophylactic treatment scheme for Prophylactic Treatment Phase II: Calculated schemes
Appendix SeqPK 1	Graphs and WinNonlin outputs for individual PK Analysis (sequential during study) - Human-cl rhFVIII – One-stage assay
Appendix SeqPK 2	Simulation of elimination curve for multiple dosing in individually tailorized prophylactic treatment scheme for Prophylactic Treatment Phase II. – One-stage assay *(Graphs and WinNonlin outputs; only in case scheme cannot be determined by analytical method because of numerical problems)*

Appendix I: Haemophilia Joint Health Score – Summary Score Sheet, Version 2.1

Reference: [2]

Subject ID #:_____ **Name of Physiotherapist:**_____

Assessment # : _____ **Date:** _____
yyyy / mm / dd

Time: _____

Hemophilia Joint Health Score 2.1 - Summary Score Sheet

	Left Elbow		Right Elbow		Left Knee		Right Knee		Left Ankle		Right Ankle	
Swelling		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Duration (swelling)		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Muscle Atrophy		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Crepitus on motion		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Flexion Loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Extension Loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint Pain		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Strength		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint Total												

Sum of Joint Totals + ☐

Global Gait Score ☐

(☐ NE included in Gait items)

HJHS Total Score = ☐

NE = Non-Evaluable

Swelling
0 = No swelling
1 = Mild
2 = Moderate
3 = Severe

Duration
0 = No swelling or < 6 months
1 = ≥ 6 months

Muscle Atrophy
0 = None
1 = Mild
2 = Severe

Crepitus on Motion
0 = None
1 = Mild
2 = Severe

Flexion Loss

	Contralateral:	Normative Tables:
0	= < 5°	0= within range
1	= 5° - 10°	1 = 1° - 4°
2	= 11° - 20°	2 = 5° - 10°
3	= > 20°	3 = > 10°

Extension loss (from hyperextension)

	Contralateral:	Normative tables:
0	= < 5°	0= within range
1	= 5° - 10°	1 = 1° - 4°
2	= 11°- 20°	2 = 5° - 10°
3	= > 20°	3 = > 10°

Joint Pain
0 = No pain through active range of motion
1 = No pain through active range; only pain on gentle overpressure or palpation
2 = Pain through active range

Strength (Using The Daniels & Worthingham's scale)
Within available ROM
0 = Holds test position against gravity with maximum resistance (gr.5)
1 = Holds test position against gravity with moderate resistance (but breaks with maximal resistance) (gr.4)
2 = Holds test position with minimal resistance (gr. 3+), or holds test position against gravity (gr.3)
3 = Able to partially complete ROM against gravity (gr.3-/2+), or able to move through ROM gravity eliminated (gr.2), or through partial ROM gravity eliminated (gr.2-)
4 = Trace (gr.1) or no muscle contraction (gr.0)
NE = Non-evaluable

Global Gait (walking, stairs, running, hopping on 1 leg)
0 = All skills are within normal limits
1 = One skill is not within normal limits
2 = Two skills are not within normal limits
3 = Three skills are not within normal limits
4 = No skills are within normal limits
NE = Non-evaluable

NOTE: There is an accompanying instruction manual and worksheets that are required when administering the HJHS

General Comments:

_____
_____
_____
_____

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