	Statistical Analysis Plan
Study JD	GENA-15
Study title	Extension Study for Patients who completed GENA-05 (NuProtect) to Investigate Immunogenicity, Efficacy and Safety of Treatment with *Human-cl rhFVIII*

Document type	SAP
Document ID	2959 **(GENA-15-SAP)**
Document version	2.00
Effective date	2019-04-30

Supersedes document	1.00
Reason for change	Additional sub-analyses added (annualized bleeding rate (ABR)), definition for populations updated according to protocol Appendix 1 (Transformations/Derivations) updated, further minor changes

Protocol (version) this SAP is **based** upon	Clinical study protocol GENA-15, V 02 dated 2018-04-23

Purpose	The Statistical Analysis Plan describes the statistical analyses to be performed on study GENA-15 in full detail, and the resulting output that will be compiled in the clinical study report

Attachments

Approved by

Name and function | Date and signature

[redacted]

Table of contents

Glossary

Term	Description
ABR	Annualized bleeding rate
AE	Adverse event
ATC	WHO drug dictionary anatomic therapeutic classification
BE	Bleeding episode
BHK	Baby hamster kidney (cells)
BLEED	Study population of BEs
BLEED-PP	All documented bleeds in the BLEED population of subjects in the per protocol (PP) population
BMI	Body mass index
BPWP	Blood products working party
BU/mL	Bethesda unit per milliliter
BW	Body weight
CHO	Chinese hamster ovary (cells)
CHMP	Committee for medicinal products for human use
CSR	Clinical study report
DNA	Deoxyribonucleic acid
EC	Ethics committee
ED	Exposure day
EMA	European medicines agency
FVIII	Coagulation factor VIII
FVIII:C	Factor VIII coagulation activity
HEK	Human embryonic kidney
Human-cl rhFVIII	Human cell line derived recombinant human FVIII
ICH	International conference on harmonisation
IMP	Investigational medicinal product
ITI	Immune tolerance induction
ITT	Intention to treat
IU	International unit
MedDRA	Medical dictionary for regulatory activities
OD	On-demand
PP	Per protocol
PROPH	Study population of subjects with prophylaxis
PT	Preferred Term (MedDRA)
PTPs	Previously treated patients
PUPs	Previously untreated patients
rFVIII	Recombinant FVIII
SAEs	Serious adverse events
SAF	Safety population
SAP	Statistical analysis plan
SOC	System Organ Class (MedDRA)
SURG	Study population of surgeries
SURG-PP	Surgical interventions of subjects in the per protocol (PP) population
TBD	To be determined
WHO	World health organization

1. Introduction / Objectives

1.1. Introduction

Haemophilia A is an inherited gender-related coagulation disorder in which affected persons (mainly males) do not produce functional coagulation factor VIII (FVIII) in sufficient quantities to achieve satisfactory haemostasis. Therefore, patients suffer from bleeding diathesis. Most bleeding episodes (BEs) occur in joints and muscles. Without adequate treatment, repeated haemarthroses and haematoma can lead to long-term sequelae with severe disability. Other bleeding sites, although less frequent but more severe, are the central nervous system, the urinary or gastrointestinal tract, eyes and the retro-peritoneum. Hence, affected patients are at high risk to develop major and life-threatening bleeds after surgical procedures, even after minor ones such as tooth extraction. An optimal and effective treatment of the disorder is the replacement of FVIII by using FVIII concentrate either obtained by fractionation of human plasma or manufactured by recombinant DNA technology.

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

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

1.2. Study Objectives

The present study has been designed to investigate the long-term immunogenicity, tolerability and efficacy of *Human-cl rhFVIII* in patients originally included into the preceding study GENA-05 as PUPs with severe haemophilia A (FVIII:C <1%).

The objectives of the study are to

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

2. Design

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

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

The occurrence of adverse events (AEs) and changes in concomitant medication will be checked and documented at each follow-up visit. A patient completes the study by switching to marketed investigational medicine product (IMP), but not later than 2 years after his screening visit.

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

The study was clinically started in the 1st quarter of 2014 and continued until the 4th quarter of 2018.

3. Endpoints

3.1. Immunogenicity Endpoints

Immunogenicity of *Human-cl rhFVIII* will be assessed by monitoring FVIII inhibitor activity. Inhibitor activity will be determined at the following time points:

- At Screening Visit, which will most probably be identical to the completion visit of GENA-05
- Once every 6 months in the course of the follow-up visits
- At Study Completion
- Any time in the case of a suspicion of inhibitor development.

In case of a positive inhibitor result (≥ 0.6 BU/mL), an inhibitor retesting, using a second separately drawn sample, should be performed. A FVIII inhibitor is defined as “positive”, if the retesting confirms the positive result, otherwise the result is considered as “negative”.

3.2. Efficacy Endpoints

Efficacy of prophylactic treatment

The efficacy of *Human-cl rhFVIII* in the prophylactic treatment will be investigated by calculating the frequency of spontaneous break-through bleeds under prophylactic treatment. Study drug consumption data (FVIII IU/kg per month, per year) per patient and in total will be evaluated.

Efficacy of treatment of bleeds

The efficacy of *Human-cl rhFVIII* in the treatment of bleeds will be investigated by using a 4-point ordinal haemostatic efficacy scale, which will be made by the patient’s parent(s)/legal guardian(s) (together with the Investigator in case of on-site treatment). Details of the bleed, the amount of *Human-cl rhFVIII* needed and the number of injections necessary to stop the bleed will be evaluated.

Efficacy of surgical prophylaxis
In surgical procedures, the following parameters will be documented:

- One overall efficacy assessment (taking into account the intra- and post-operative assessment) after the end of surgical prophylactic treatment phase, agreed upon between the surgeon and the haematologist
- Average and maximum expected estimated blood loss, compared to the actual estimated blood loss
- Details on surgical procedure: location, severity, type, expected and actual duration
- Pre-, intra-, and post-operative FVIII plasma levels, if available
- Details of administered dose(s) of *Human-cl rhFVIII* given pre-, intra- and/or post-operatively including dates, times and batch numbers
- Details on concomitantly administered drugs, including all blood and blood product transfusions, excluding standard anaesthetic drugs
- Details on all wound haematomas including any need for surgical evacuation will be evaluated
- Outcome of the intervention, described by means of a brief narrative.

3.3. Safety Endpoints

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

4. Analysis Populations

4.1. Overall Subject Level Populations

For the analysis of this study the following three general subject populations will be considered:

SAF: All subjects who received at least one dose of *Human-cl rhFVIII.*
ITT: All subjects in the safety analysis population for whom any data was collected post treatment with *Human-cl rhFVIII*.
PP: All subjects in the ITT analysis population who completed the trial without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the efficacy results.

Especially, subjects meeting any of the following criteria will be excluded from the PP analysis:

- did not complete the GENA-05 trial regularly,
- use of concomitant medication that may confound study results,
- exhibit significant non-compliances with the protocol like for example non-compliance to complete the diary in a proper manner or more than 30% of haemostatic efficacy assessments missing.
- present dosing or treatment errors like the use of other FVIII products (except for emergencies) or several unexplained and significant deviations from the recommended dose regimen.

4.2. Subject Level Sub-Populations

Due to the different treatment regimens and reasons for treatment the following sub-populations will be considered in the analysis:

PROPH: All subjects in the ITT population who have at least one prophylactic treatment. Only data under prophylaxis will be used for the analyses.

PROPH-PP: All subjects in the PP population who have no significant dosing or treatment errors like e.g. unexplained interruptions of the prophylaxis with *Human-cl rhFVIII*

OD: All subjects who have at least one on-demand treatment. Only data under on-demand treatment will be used for the analyses.

4.3. Event-Level Populations

BLEED: All documented bleeding episodes (spontaneous, traumatic, post-operative or other) for which any amount of treatment with *Human-cl rhFVIII* is documented until the completion visit

BLEED-PP: All documented bleeds in the BLEED population of subjects in the PP population

SURG: All documented surgical interventions 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

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

4.4. All Populations

The subject disposition, i.e. the identification of significant deviations to be considered for exclusion from the PP population and the assignment of each subject, bleeding and surgery to the respective analysis populations, will be the joint decision of the study statistician and the responsible medical expert prior to database lock.

Considering the different study objectives, it has been decided that

- the ITT population is considered to be the most relevant for the analysis of immunogenicity data,
- the PROPH population is considered to be the most relevant for the analysis of efficacy data on prophylaxis,
- the BLEED population is considered to be most relevant for the analysis of efficacy data on bleedings,
- the SURG population is considered to be the most relevant for the analysis of efficacy data on surgeries.

To evaluate the robustness of the study results, efficacy analyses will also be done on basis of the PP (sub-) population.

5. Statistical Methods

Please refer to appendix 2 for a detailed description of tables (marked “T”), listings (“L”) and figures (“F”).

Due to the fact that this study is an extension of the study GENA-05 and subjects will enter this study immediately after completion of their final visit in study GENA-05, subject data from study GENA-05 will be used in the analysis. Especially, this applies to the use of demographic data and other background subject characteristics. Also, whenever screening or baseline values are required for comparisons or the assessment of changes (e.g. laboratory measurements) these values will be taken from the last available values in study GENA-05, unless more recent measurements were obtained in the present study.

5.1. General Presentation

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 subjects in the analysis population (N) and the number of subjects contributing to each particular summary (n) will be included in every presentation.
Where appropriate, results will be presented grouped by different subject characteristics, such as bleeding sites or surgery types, as well as in total.

- 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
- Time-to-event data (how long it takes to observe the outcome of interest, e.g. the development of inhibitors to FVIII): time to event or last evaluation (censored data in case subjects are lost to follow-up) and event rate. These parameters might not be tabulated separately, but can be included as an inset into a Kaplan-Meier plot of the product-limit survival function estimates.

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

Figures

Figures will always reference the number of subjects 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 mean $\pm$ standard deviation over time points may be used to illustrate the statistical outcome.

Listings

For selected results statistical summarization alone seems inappropriate, and listings will be presented to facilitate in-depth review of the data; these include (but are not limited to):

- AE
- Reason for withdrawal
- IMP consumption
- Details on inhibitors

In addition, all individual data will be presented in the individual subject data listings to be appended to the clinical study report (CSR) as section 16.2.

5.2. Statistical Concept

5.2.1. Efficacy Analysis

Efficacy will be evaluated by descriptive statistics.

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

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

5.2.2. Safety Analysis

Immunogenicity

All recorded determinations of inhibitors against FVIII will be listed. The occurrence and cumulative incidence of inhibitors (inhibitor titer ≥0.6 and ≥5 BU/mL respectively) will be presented in total, and as percentage of the analysis population with a 95% confidence interval.

If justified by the number of events, the time period until the first inhibitor activity will be tabulated and displayed graphically by means of a Kaplan-Meier plot of percentages without inhibitor versus cumulative EDs until appearance of inhibitor.

The number of EDs before inhibitor development will be tabulated for each patient who develops FVIII inhibitors.

Adverse events (AEs)

All AEs occurring after initiation of study treatments (including events likely to be related to the underlying disease, or a concomitant illness or medication or clinical significant abnormalities in laboratory parameters or vital signs) will be displayed in summary tables and listings.
Incidences of AEs will be given as numbers and percentages of patients with:

- Any AE
- Any serious AE (SAE)
- Any AE probably or possibly related to the trial drug
- Any AE that begins within 24 hours of the end of an infusion
- Any severe AE
- Any withdrawal due to AE
- Any AE by MedDRA SOC and PT

Summary tables for AEs will be given by SOC and preferred term. Additionally, AEs will be summarized by severity and relationship to study treatment.

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

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

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

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

5.2.3. Other Analyses

All demographic data and other baseline characteristics (e.g. medical history and concomitant medications) will be presented in summary and/or frequency tables and will be listed in section 16.2.

5.3. Interim Analysis

No interim analysis is planned.

5.4. Subgroup Analysis/Event-Level Analysis

Parts of the analyses will be performed in the sub-populations defined in section 4.2 depending on the number of subjects per sub-population.
Event-level analysis will be performed for bleeding and surgery populations depending on the number of events per population.

5.5. Imputation of Missing Data

In general missing data values will not be imputed, except for the following situations:

- Body weight (BW): In case of missing weight, the last available weight measurement will be used for calculation of dosing (last observation carried forward)
- Calculation of age in case day of birth is missing “15” for day will be imputed
- Subjects who permanently switch to another FVIII product during their study participation 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 subjects who switch to another FVIII product during their study participation will **not** be considered treatment failures in the efficacy analyses:

  a) if the administration of another FVIII concentrate was due to an emergency situation,
  b) if the IMP was not available for the patient in time.

  In these two cases the efficacy will be considered a missing value with regard to *Human-cl rhFVIII.*

- Efficacy evaluation by the surgeon and the haematologist at the end of the surgery and on the last post-operative day (end of post-operative phase):

- Subjects 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 available at the site; in this case the efficacy will be considered a missing value with regard to *Human-cl rhFVIII.*

A complete list of dropouts (subjects prematurely ending the study) will be presented, including the reason for premature discontinuation of the study and the duration of participation in the trial in terms of total days as well as EDs.

5.6. Software used

The SAS system (version 9.4 or later) will be used for all computations, tables, figures and listings.

6. Data Derivations and Data Transfer

Apart from summarizing the doses of the IMP over different time periods and normalizing the doses by kg BW, no special derivations are planned.

The results of all data transformations and derivations will be stored in analysis data sets and transferred to the sponsor upon completion of the statistical analysis.

Laboratory data received electronically from the central laboratory will be integrated into the data base and also be transferred to the sponsor upon completion of the statistical analysis.

7. Tables, Figures and Listings

An overview of the summary tables and illustrating figures to be included in the study report of this analysis and its appendix 14 is given in appendix 2 of this SAP.

Listings of all data recorded during the study will be presented in appendix 16.2 of the study report. A detailed overview of all planned listings is included in appendix 2 of this SAP.

8. Changes from Analyses Specified in the Protocol

The following changes in analyses to the study protocol will be applied (see also Appendix 1):

- The annualized bleeding rate (ABR) will be analyzed in addition (per type of bleeding / per site of bleeding)
- The efficacy of prophylactic treatment, i.e. the frequency of break through bleedings per months by calculated frequency of prophylaxis will be stratified by frequencies “at least three times weekly”, “at least once weekly - < three times weekly” and in total (analysis planned as per protocol would be “three times weekly or every other day prophylactic treatment”)
- The “time period surgery” will be defined according to GENA-05 SAP: Time period between start of surgery-related prophylactic treatment and re-start of prophylactic treatment after surgery (GENA-15 protocol: time period from start of a surgery until final assessment of the surgery)

9. References

(1) Kobayashi T, and Ezzelarab M. Glycobiology relating to xenotransplantation. Curr Opin Organ Transplant 2006; 11: 1541-59.

(2) Hokke CH, Bergwerff AA, van Dedem GWK, van Oostrum J, Kamerling JP, and Vliegenthart JFG. Sialylated carbohydrate chains of recombinant human glycoproteins expressed in Chinese hamster ovary cells contain traces of Nglycolylneuraminic acid. FEBS Lett 1990; 275: 9-14.

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

(4) Kannicht Ch, Ramström M, Kohla G, Tiemeyer M, Casademunt E, Walter O, Sandberg H. Characterisation of the post-translational modifications of a novel, human cell line-derived recombinant human factor VIII. Thrombosis Research 2013, 131: 78–88

(5) Guideline on the clinical Investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev. 2), London, 01 Feb 2019

(6) Ethical Considerations for Clinical Trials on Medicinal Products conducted with the Paediatric Population. Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use, Final 2008

Other documents	Description
ICH Topic E3	Structure and Content of Clinical Study Reports
ICH Topic E9	Statistical Principles for Clinical Trials

Appendix 1 Transformations / Derivations

Formulas for derived variables

Variable	Description
Annualized bleeding rate (ABR)	Total number of bleedings during study/time in study (years) (per type of bleeding / per site of bleeding)
Average total consumption (all and bleeding)	Total IMP dose administered/time in study (per year) This applies to IMP consumption for all reasons of administration as a whole (prophylaxis, bleeding, surgery) as well as separately for reason = 'Bleeding'
Average total consumption (prophylaxis)	Total IMP dose administered/time under prophylaxis
Durations between two dates	Later date minus earlier date plus 1, expressed in days. (Remark: Duration will be 1, if both dates are the same)
Frequency of break through bleedings per month	Total number of bleedings under prophylaxis (bleedings occurring under time period of surgery will not be counted) / time under prophylaxis (days) / 365.25*12 by calculated frequency of prophylaxis (see below)
Frequency of prophylactic treatment (per week)	Number of prophylactic treatments / time under prophylaxis (days) / 7 (stratified by calculated frequencies "at least three times weekly", "at least once weekly - < three times weekly" and in total) Note: different from protocol (per protocol to be analyzed for three times weekly or every other day prophylactic treatment))
Time in Study	Days: date of completion (i.e. end of observational period) – date of screening visit +1 (days) Months: (date of completion (i.e. end of observational period) – date of screening visit +1)/365.25*12 Years: (date of completion (i.e. end of observational period) – date of screening visit +1)/365.25
Time under Prophylaxis (in days)	(Last prophylactic treatment – first prophylactic treatment + 1) + 2 days Or completion visit – first prophylactic treatment + 1) whichever comes first - Time periods for surgery - Time periods under 'On demand treatment' (not applicable)
Time period surgery (in days)	Time period between start of surgery-related prophylactic treatment and restart of prophylactic treatment after surgery (i.e. first prophylactic treatment after surgery – 1). Note: Calculation adapted to GENA-05. (GENA-15 protocol: time period from start of a surgery until final assessment of the surgery)
ED	Each calendar day the subject received IMP
Administered Dose (IU/kg)	Documented dose (IU / kg BW)

Efficacy Assessment of Prophylactic Treatment

The efficacy of *Human-cl rhFVIII* in prophylactic treatment will be evaluated based on the frequency of spontaneous breakthrough bleeds per months under prophylaxis for frequencies of Human-cl rhFVIII administration “at least three times weekly”, “at least once weekly” and in total and will be assigned as follows:

Efficacy	**Definition**
Excellent	< 0.75 spontaneous BEs per month
Good	0.75 - 1 spontaneous BEs per month
Moderate	> 1 and ≤ 1.5 spontaneous BEs per month
Poor	> 1.5 spontaneous BEs per month

Appendix 2 Tables, Figures and Listings details

The tables below contain a detailed description of the output to be produced (tables, figures, listings and other outputs) for the study conclusion. The type of generated output is abbreviated by the following letter:

T = Summary Table F = Figure L = Subject Listing

All output will be headed with an appropriate heading specifying study ID and title.
All output will be dated and have page numbers in the form 'Page [x / y]'.
All statistical output will identify the underlying analysis populations, and indicate the number of subjects / events in this population (N) and the number of subjects/events actually contributing to the particular output (n).

Tables

No.	T/F/L	Description	Pop.
Section 14 Tables, figures and listings referred to but not included in the text			
Section 14.1 Demographic Data			
	T	Subject disposition and analysis populations Number of subjects enrolled, erroneously enrolled, treated, completed, prematurely discontinued	All
	T	Protocol Deviations Frequency of protocol violations by “minor” and “major” and in total	All
	T	Number of subjects per center	SAF
	T	Statistics on age, body height, body weight, body mass index (BMI)	SAF
	T/L	Statistics on study participation (first- and last treatment, duration of treatment, EDs)	SAF
	T	Bethesda assay results (BU/mL) at screening	SAF
	T	Frequency of use of prior and concomitant medications by ATC class	SAF
	T	Frequency of new medical history conditions by SOC and PT	SAF
Section 14.2 Efficacy Data			
	T	Statistics on incidence of inhibitors (≥0.6 and ≥5 BU/mL) with 95% conf. interval	ITT, PP
	L	Listing of details on patients with inhibitors	ITT, PP
	T	Statistics on time to first inhibitor activity	ITT, PP
	F	Kaplan-Meier curves on time to first inhibitor activity	ITT, PP
	T	Frequency distribution of prophylactic schedules	PROPH, PROPH-PP
	T	Statistics on the number of EDs for prophylactic treatment and dosages administered	PROPH, PROPH-PP
	T	Statistics on the amount of *Human-cl rhFVIII* (IU) for prophylactic treatment per month, per year, per EDs, per injection and in total	PROPH, PROPH-PP
	T	Statistics on the dosage of *Human-cl rhFVIII* (IU/kg) for prophylactic treatment per month, per year, per EDs, per injection and in total	PROPH, PROPH-PP
	T	Prophylactic Treatment *basic summary statistics on prophylactically treated subjects (dosing, pattern), changes/interruptions of prophylactic treatment*	PROPH, PROPH-PP

No.	T/F/L	Description	Pop.
	T	Overall Efficacy Assessment of Prophylactic Treatment (Monthly rate of BEs with 95% confidence interval) – spontaneous BEs *summary statistics on the number and rate of BEs per type of BE, per site of BE, per severity of BE, per grouped time intervals from last administered dose*	PROPH, PROPH-PP
	T	Overall Efficacy Assessment of Prophylactic Treatment (Monthly rate of BEs with 95% confidence interval) – traumatic BEs *summary statistics on the number and rate of BEs per type of BE, per site of BE, per severity of BE, per grouped time intervals from last administered dose*	PROPH, PROPH-PP
	T	Overall Efficacy Assessment of Prophylactic Treatment (Monthly rate of BEs with 95% confidence interval) – all BEs *summary statistics on the number and rate of BEs per type of BE, per site of BE, per severity of BE, per grouped time intervals from last administered dose*	PROPH, PROPH-PP
	T	Number of EDs and dosages administered for on demand treatment with *Human-cl rhFVIII*	OD, OD-PP
	T	Statistics on the number of EDs for on demand treatment to *Human-cl rhFVIII* and dosages administered	OD, OD-PP
	T	Statistics on the amount of *Human-cl rhFVIII* (IU) for on demand treatment per month, per year, per EDs, per injection and in total	OD, OD-PP
	T	Statistics on the dosage of *Human-cl rhFVIII* (IU/kg) for on demand treatment per month, per year, per EDs, per injection and in total	OD, OD-PP
	T	On demand: Statistics on changes in treatment of BEs	OD, OD-PP
	T	On demand: Frequency table on haemostatic agents used under on demand	OD, OD-PP
	T	Number and frequency of BEs per year per subject (ABR) per type and site of bleeding	BLEED, BLEED-PP
	T	Frequency of BEs per site of BE and in total	BLEED, BLEED-PP
	T	Frequency of BEs per type of treatment at start of BE (prophylactic, on demand)	BLEED, BLEED-PP
	T	Severity of BEs per type of BE (spontaneous, traumatic, post-operative, other) and in total	BLEED, BLEED-PP
	T	Severity of BEs by site of BE (Frequency counts)	BLEED, BLEED-PP
	T	Treatment duration for BEs per severity and in total	BLEED, BLEED-PP
	T	Personal efficacy assessment (final outcome) of treatment of bleeding episode per severity and in total	BLEED, BLEED-PP
	T	Statistics on the number of EDs to *Human-cl rhFVIII* and dosages administered	BLEED, BLEED-PP
	T	Statistics on dose (IU and IU/kg BW) and number of infusions per bleeding episode, per bleeding site and in total	BLEED, BLEED-PP
	T	Statistics on dose (IU and IU/kg BW) per bleeding episode by severity of BE and efficacy	BLEED, BLEED-PP

No.	T/F/L	Description	Pop.
	T	Statistics on dose (IU and IU/kg BW) of *Human-cl rhFVIII* per infusion per bleeding site and in total	BLEED, BLEED-PP
	T	Statistics on dose (IU and IU/kg BW) of *Human-cl rhFVIII* per ED per bleeding site and in total	BLEED, BLEED-PP
	T	Statistics on dose (IU and IU/kg BW) of *Human-cl rhFVIII* per infusion per BE per severity of BE and in total	BLEED, BLEED-PP
	T	Statistics on dose (IU and IU/kg BW) of *Human-cl rhFVIII* per month and per year for bleeding episodes	BLEED, BLEED-PP
	T	Number of treatment days needed to stop a bleed (per BE)	BLEED, BLEED-PP
	T	Frequency of dose changes* per number of BEs and per number of infusions *in the doses (in IU/kg BW) per infusion and changes in the total dose used to treat subsequent BEs of the same site (e.g. elbow, knee, etc.) in the same patient. A dose change will be counted only if the difference in the weight adjusted doses is ≥ 30 IU/kg BW	BLEED, BLEED-PP
	T	Frequency of dose changes (in IU/kg BW) for same site of BE per number of BEs and per number of infusions by site of BE	BLEED, BLEED-PP
	T	Subjects included in surgery analysis and number of surgical procedures (minor, major, total)	SURG, SURG-PP
	L	Surgery Characteristics basic summary statistics on type, (not) planned, severity, duration	SURG, SURG-PP
	T	Efficacy Evaluation in Surgical Procedures a) at end of surgery by surgeon b) overall post-operatively by surgeon as well as by haematologist Statistics on the efficacy evaluations made by the surgeon and the haematologist on i) Four point scale (excellent, good, moderate, none) ii) Three point scale (excellent/good (successful), moderate, none)	SURG, SURG-PP
	T	Frequency of use of concomitant medications by ATC class during surgery	SURG, SURG-PP
	T	Statistics on number of infusions and EDs for surgeries per severity and in total	SURG, SURG-PP
	T	Statistics on total dose of *Human-cl rhFVIII* (IU, IU/kg BW, IU/kg BW and ED, IU per infusion, IU/kg BW and infusion) for surgeries per severity and in total	SURG, SURG-PP
	T	Statistics on pre-operative loading dose before surgery (IU and IU/kg BW)	SURG, SURG-PP
	T	Statistics on infusions administered during the surgery (Maintenance doses)	SURG, SURG-PP
	T	Statistics on infusions administered after end of the surgery	SURG, SURG-PP
	T	Statistics on expected (average and maximum), actual blood loss and difference between expected and actual blood loss	SURG, SURG-PP
	T	Statistics on expected and actual duration of the surgical procedure and difference between expected and actual duration	SURG, SURG-PP

No.	T/F/L	Description	Pop.
Section 14.3 Safety Data			
Section 14.3.1 Display of Adverse Events (AEs)			
	T	Summary of AEs by SOC and PT number of subjects/infusions with any AE	SAF
	T	Treatment-emergent AEs by SOC and PT	SAF
	T	Treatment-emergent related AEs by SOC and PT	SAF
	T	Treatment-emergent AEs by severity, SOC and PT	SAF
	T	Treatment-emergent AEs by SOC and PT, stratified by severity and relationship *grouped by age, sex, EDs, amount of Human-cl rhFVIII (including EDs and amount used within GENA-05)*	SAF
	T	Summary of AEs – after surgical interventions (up to end of post-surgical treatment)	SURG
	T	Treatment-emergent AEs by SOC and PT after surgical interventions (up to end of post-surgical treatment)	SURG
Section 14.3.2 Listings of Death, Other Serious and Significant Adverse Events (SAEs)			
	T	Treatment-emergent SAEs by system organ class and preferred term	SAF
	L	Detailed listing of SAEs	SAF
	L	Detailed listing of deaths	SAF
	L	Detailed listing of AEs leading to discontinuation of study medication	SAF
Section 14.3.3 Narratives of Deaths and Other Serious Adverse Events			
	L	To be included in section 12.3.3 of the CSR	
Section 14.3.4 Other Safety Parameters			
	T	Abnormal laboratory value listing	SAF
	T	Safety Lab Panel *summary statistics for each lab parameter and time point (excluding surgery)*	SAF
	T	Safety Lab Panel *Change in lab parameter from baseline per time point (excluding surgery)*	SAF
	T	Safety Lab Panel *summary statistics for each lab parameter before surgery, after surgery and change*	SURG
	T	Vital Signs *Summary statistics on all vital signs per time point (excluding surgery)*	SAF
	T	Vital Signs*: Summary statistics on changes in vital signs compared to baseline per time point (excluding surgery)*	SAF
	T	Vital Signs *Summary statistics on all vital signs per time point before, during and after surgery*	SURG
	T	Vital Signs *: Summary statistics on changes in vital signs during and after surgery compared to before surgery*	SURG
	T	Physical Examination shift tables on the evaluations of each category (baseline vs. monthly visits)	SAF

Lists

No.	T/F/L	Description	Pop.
Section 16.2 *Subject Data Listings*			
Section 16.2.1 Discontinued patients			
	L	Prematurely discontinued subjects (incl. time in study, reason for premature discontinuation, age, total dose, total dose per kg BW and number of EDs)	All
	L	Study completion	All
Section 16.2.2 Protocol deviations			
	L	Protocol violations and data issues *flagged by "minor" and "major"*	All
Section 16.2.3 Patient disposition			
	L	Disposition of subjects with respect to analysis populations	All
Section 16.2.4 Demographic data and other baseline data			
	L	Subject demographics	SAF
	L	Medical history	SAF
	L	Other baseline data	SAF
	L	Prior and concomitant medication	SAF
	L	Relevant concomitant medication in ATC class blood and blood forming organs	SAF
	L	Concomitant medication used in the treatment of BEs	BLEED
	L	Concomitant medication during surgery	SURG
	L	Concomitant medication in ATC class blood and blood forming organs during hospitalization for surgery	SURG
Section 16.2.5 Compliance and/or drug concentration data			
	L	*Human-cl rhFVIII* doses during study including reason for treatment	SAF
	L	Number of infusions and *Human-cl rhFVIII* consumption per ED	SAF
	L	Subject exposure (duration of participation, EDs, number of infusions)	SAF
	L	Doses of *Human-cl rhFVIII* for on demand therapy	OD
	L	*Human-cl rhFVIII* injections for prophylactic treatment during study	PROPH
	L	EDs and *Human-cl rhFVIII* consumption for prophylactic treatment during study	PROPH
	L	Amount of *Human-cl rhFVIII* per month, per year, per prophylactic treatment episode, ED and in total	PROPH
	L	Dose of *Human-cl rhFVIII* for surgical reasons	SURG
	L	Pre-, intra-, and post-operative FVIII:C plasma levels (local and central lab)	SURG
Section 16.2.6 Individual efficacy response data			
	L	Number of BEs, rate per month, rate per year, overall efficacy of prophylactic treatment, characteristics of BE	BLEED
	L	Number of BEs, rate per month, rate per year	BLEED

No.	T/F/L	Description	Pop.
	L	BEs during study (incl. prophylactically treated yes/no, efficacy assessment of treatment)	BLEED
	L	BEs, doses and changes in dose per infusion for each bleeding episode during study	BLEED
	L	Intensity of treatment prior to bleeding event (BE site, severity, duration of BE, last treatment prior to onset, total dose/kg administered within the week prior to bleeding event)	BLEED
	L	BEs by site of BE, efficacy assessments, doses and changes in dose per BE and per infusion by site of BE	BLEED
	L	Other per subject data on BEs in BLEED population	BLEED
	L	Statistics on individual dose changes between subsequent BEs, and between subsequent BEs of the same site	BLEED
	L	Changes in dose between subsequent BEs, changes in dose between subsequent BEs of the same site	BLEED
	L	Surgeries: Description and outcome of surgical procedures	SURG
	L	Surgeries: Description of wound hematoma yes/no and whether it needed surgical evacuation yes/no	SURG
	L	Surgeries: Description and assignment to SURG/SURG-PP populations including reasons for exclusion	SURG
	L	Surgeries: Blood loss (planned and actual), duration of surgery (planned and actual)	SURG
Section 16.2.7 Adverse event listing			
	L	AEs	SAF
	L	Possibly/probably related AEs	SAF
	L	Non-treatment emergent AEs	SAF
Section 16.2.8 Listing of laboratory measurements			
	L	Laboratory assessments (Haematology, Clinical chemistry)	SAF
	L	FVIII:C, Inhibitors at baseline and during study	SAF
	L	Occurrence of inhibitor and time to inhibitor occurrence and number of EDs before inhibitor development, if any	SAF
Section 16.2.9 Other safety data			
	L	Additional comments provided in the CRF	SAF
	L	Vital signs	SAF
	L	Physical examination	SAF
	L	Abnormal findings of physical examination	SAF

In-text tables and figures

No.	T/F/L	Description
Section 11 Efficacy Evaluation		
	T/F	TBD
Section 12 Safety Evaluation		
	T/F	TBD

Appendix 3 Further Details on Statistical Methods

No further statistical details, statistical analysis will primarily be descriptive.