STATISTICAL ANALYSIS PLAN
GENA-05

Immunogenicity, Efficacy and Safety of Treatment with *Human-cl rhFVIII* in Previously Untreated Patients with Severe Haemophilia A

Development Phase III

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The following approved this document:

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1 PURPOSE

This Statistical Analysis Plan describes all* statistical analyses to be performed on data collected in study GENA-05* in full detail, and the resulting output that will be compiled for the integrated clinical and statistical report.

No inferential statistics but explorative and descriptive statistics only are planned for this uncontrolled trial.

The 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 the SAP:

The CSR will include

- Tables, figures and listings included in or referred to but not included in the text of the CSR (section 14 of the CSR)
    - Demographic Data Summary figures and tables
    - Efficacy Data Summary figures and tables
    - Safety Data Summary figures and tables
- Listings provided as appendices to the CSR
    - Subject Data Listings (section 16.2 of the CSR)
    - Individual Subject Data Listings (section 16.4 of the CSR) will be covered by inclusion of SAS datasets into the electronic submission to the authorities

Please refer to section 13 of this SAP for details on the tables, figures and listings produced.

*RNA expression analysis data and Antitope Ltd. sub-study data generated in the study will not be analysed under this SAP.

2 INTRODUCTION

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

The optimal effective treatment of the disorder is the replacement of FVIII by using FVIII concentrate either obtained by fractionation of human plasma or manufactured by recombinant DNA technology. However, the occurrence of inhibitory antibodies against the infused FVIII is a major clinical complication in the treatment of haemophilia A. Data from a prospective, randomized, controlled trial, SIPPET, (Peyvandi et al. NEJM 2016), published while the GENA-05 study was ongoing, showed a cumulative inhibitor incidence of 44.5% in PUPs and minimally treated patients treated with rFVIII (all derived from hamster cell lines) compared with 26.8% in patients treated with pdFVIII/VWF products. In the SIPPET study, no inhibitors developed in PUPs with non-null mutations in the *F8* gene following treatment with pdFVIII/VWF concentrates; whereas 43% of patients with null mutations in the *F8* gene developed inhibitors in the rFVIII group.

Human-cl rhFVIII is a B-domain deleted rhFVIII expressed in genetically modified human embryonic kidney (HEK) 293F cells. Using a human cell line for the expression of rFVIII ensures that non-human immunogenic epitopes are absent, in contrast to rFVIII expressed in hamster cells. 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 previously treated patients (PTPs) are available. Since paediatric patients may respond differently to FVIII treatments than adults, European Medicines Agency (EMA) CHMP guidelines [1] applicable at the time the GENA-05 study was initiated specify that paediatric studies should be conducted within the clinical investigation program of FVIII products. Moreover, the clinical development strategy for FVIII products in paediatric patients should follow a stepwise approach, in order to gain experience in older patients before investigations are initiated in younger patients. Study GENA-03 was assessing efficacy, immunogenicity, pharmacokinetic profiles and safety of *Human-cl rhFVIII* in paediatric patients between 2 and 12 years. With the availability of 6 months' treatment data from more than 20 previously treated children, and with having finished all baseline pharmacokinetic assessments, the present study has been designed to investigate the immunogenicity, efficacy and safety of *Human-cl rhFVIII*, in previously untreated patients (PUPs) with inherited severe haemophilia A.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this clinical study is to investigate the immunogenicity of *Human-cl rhFVIII* in 100 previously untreated patients (PUPs) suffering from severe haemophilia A (FVIII:C < 1%).

3.2 Secondary Objectives

•To assess the efficacy of *Human-cl rhFVIII* during prophylactic treatment (based on the frequency of spontaneous break-through bleeds)

•To assess the efficacy of *Human-cl rhFVIII* during treatment of bleeds

•To assess the efficacy of *Human-cl rhFVIII* in surgical prophylaxis

•To assess the safety and tolerability of *Human-cl rhFVIII*

3.3 Further Objectives

•To examine the resource use of patients treated with *Human-cl rhFVIII*.

•And, if the size of the subgroups allow:

- To examine the resource use of patients treated prophylactically and patients treated on-demand.
- To examine the resource use of patients who developed inhibitors and those patients who did not develop inhibitors.

3.4 Assessment of Objectives

3.4.1 Immunogenicity

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

The *primary endpoint* is the incidence of inhibitors within the observation period. For one patient an inhibitor is assessed to be positive if the modified Bethesda assay (Nijmegen modification) results in a titer ≥ 0.6 BU at any time point during the observation period.

Inhibitor activity will be determined centrally at the following time points: At baseline (Screening Visit), every 3-4 EDs until ED 20, every 10-12 EDs or every 3 months ± 2 weeks after ED 20 (whichever comes first), at study completion; at any time in the case of a suspicion of inhibitor development.

In case of a positive inhibitor result, an inhibitor re-testing using a second separately drawn sample should be performed centrally; the result of the second sample will be taken as the final result for the time point. Low titre inhibitors will be defined as ≥ 0.6 to < 5 BU, high-titre inhibitors will be defined as ≥ 5 BU.

Patients who develop a non-transient inhibitor will have an option to start ITI treatment. Patients developing inhibitors and not starting ITI within one year after inhibitor detection will be

withdrawn from the study. Inhibitors that `disappear´ without any clinical signs or symptoms, where no FVIII dosing increase was required, and that turn back to <0.6 BU within a period of 6 months after first detection are regarded as "transient". Patients who develop such a transient inhibitor will continue regular treatment within the study until they have reached ED 100 or a maximum period of 5 years.

Definition of inhibitor confirmation and time to inhibitor occurrence:

Occurrence of inhibitors:

For these definitions inhibitor titres determined in the central laboratory are considered.

(I1) FVIII:C high titre inhibitor occurrence is confirmed, if

- inhibitor level ≥ 5BU at one time point $t_{1,H}$ and
- inhibitor level confirmed to be ≥ 5 BU at a subsequent* time point $t_{2,H}$ or
- retest of sample from *any* time point $t_{3,H}$ (=$t_{1,H}$, $t_{2,H}$ or later) confirmed to be ≥ 5 BU.

* 'Subsequent' in the context of this document always means 'at a later time point' or 'in a later sample', but not necessarily the immediate consecutive visit or sample.

(I2) FVIII:C Inhibitor occurrence in a patient is confirmed, if

- a high titre inhibitor is confirmed according to (I1)

or if

- inhibitor level ≥0.6 BU at one time point $t_{1,I}$ and retest of sample from same time point $t_{1,I}$ ≥0.6 BU and inhibitor level ≥0.6 BU at a subsequent time point

or

- inhibitor level ≥0.6 BU at one time point $t_{1,I}$ and inhibitor level ≥0.6 BU at a subsequent time point and retest of sample from same time point $t_{2,I}$ ≥0.6 BU

or

- inhibitor level ≥0.6 BU at three subsequent time points $t_{1,I}$, $t_{2,I}$ and $t_{3,I}$ (e.g. if retests are not available).

(I3) An inhibitor is confirmed to be a **low titre inhibitor**, if

- occurrence of inhibitor of < 5 BU is confirmed (according to I2) but
- occurrence of high titre inhibitor (according to I1) is *never* confirmed during the observation period*

(*Note:* a low titre inhibitor which turns to a confirmed high titre inhibitor according to definition I1 is solely counted as a high titre inhibitor. Inhibitors initially measured as low titre of < 5 BU and remain low titre (< 5 BU) are defined as low titre inhibitors)

*This condition means that a patient only can be defined as having either a low titre inhibitor or a high titre inhibitor. The patient cannot be counted twice.

These definitions for confirmation of positive inhibitors and for high and low titre inhibitors are considered to be relevant for the overwhelming number of inhibitor occurrences. However, there might be cases where additional information (e.g. when taking the whole sequence of inhibitor testing or additional local lab data into account) may suggest that an inhibitor may be assessed rather high titre than low titre. All inhibitor data will be reviewed during the Data Review Meetings before interim analysis/ final analysis to identify such cases.

Time and number of EDs until inhibitor occurrence:

(I4) The **time / number of EDs to inhibitor occurrence** is defined
- by the time between ED1 and the date of the first positive inhibitor titre detected in a confirmed inhibitor patient (I2)
- more exactly : as
  minimum {date of $t_{1,H}$, date of $t_{1,I}$} – date of Day 1 (ED1) (days) ,
  or the number of EDs (with injections for any indication) during this time frame (ED1 until day before minimum {date of $t_{1,H}$, date of $t_{1,I}$})

(*Note:* If different dates for $t_{1,H}$ and $t_{1,I}$ are available, the earlier date will be taken into account)

Censoring: Time / number of EDs until any inhibitor will be censored for patients without inhibitor at date of last available inhibitor testing

For an **analysis "time / number of EDs to inhibitor occurrence" for high titre inhibitors** the time defined under (I4) will be applied even if the inhibitor had started as minimum {date of $t_{1,H}$, date of $t_{1,I}$}. For this analysis patients with confirmed low titre inhibitor will be censored at date $t_{1,I}$, where the low titre inhibitor is first detected.

For an **analysis "time / number of EDs to inhibitor occurrence" for low titre inhibitors** the time defined under (I4) is $t_{1,I}$. For this analysis patients with confirmed high titre inhibitor will be censored at minimum {date of $t_{1,H}$, date of $t_{1,I}$}where the high titre inhibitor is first detected.

Peak inhibitor titre:

The peak inhibitor titre for each individual patient is defined as the maximum inhibitor titre measured by central lab at any timepoint during the study. This includes also the results of re-tests.

Inhibitor-free period:

An inhibitor is regarded as confirmed between start date as defined above (Definition "I4") and the time when the inhibitor titre decreases back to <0.6 BU for the first time, which is to be confirmed by a subsequent measurement of < 0.6 BU. If the inhibitor titre does not decrease to <0.6 BU during the study, the period with confirmed inhibitor will be counted until study end. Periods of time without confirmed inhibitor are regarded as "inhibitor-free".

Prophylactic Treatment

Secondary objective: To assess the efficacy of *Human-cl rhFVIII* during prophylactic treatment.

Secondary endpoint: Monthly rate of spontaneous break-through bleeds during time of prophylactic treatment assessed as excellent, good, moderate or poor by the following scale:

Excellent: Less than 0.75 spontaneous BE per month.
Good: Between 0.75 and 1 spontaneous BE per month.
Moderate: Between more than 1 and 1.5 spontaneous BEs per month.
Poor: More than 1.5 spontaneous BEs per month.

The time period for prophylactic treatment will comprise the time periods between first prophylactic treatment with *Human-cl rhFVIII* until the administration of the last prophylactic treatment + 14 days or completion visit whatever comes first) minus time periods from start of a surgery until final assessment of the surgery, and minus time period of on-demand treatment, if any. All spontaneous BEs starting during the time periods for prophylactic treatment defined above will be included. BEs categorized as traumatic or as post-operative will not be included in the primary prophylactic treatment assessment.

Regarding BEs during or after surgery this is a general rule.

However, BEs emerging shortly after surgeries could be independent from the surgery, whereas a surgery-related BE could still emerge after the final assessment of the surgery. Therefore the final assessment of whether or not the BE is related to surgery (i.e. to be categorized as post-operative), and hence will be excluded from the BE incidence calculation for prophylactic treatment, will be made in the data review meeting before final database close.

In addition to the analyses described above, the analyses of bleeding rates will be performed in all patients during inhibitor-free periods.

Study drug consumption data (FVIII IU/kg BW, extrapolated to monthly and yearly usage) per subject will be evaluated.

*3.4.2 **Bleeding Episodes (BEs)***

Secondary objective: To assess the efficacy of *Human-cl rhFVIII* during treatment of bleeds

Secondary endpoint: Efficacy assessment of bleeding episodes at end of a BE on a four point scale by the patient's parent(s)/legal guardian(s) (together with the Investigator in case of on-site treatment):

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

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

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

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

For all breakthrough BEs occurring during the study period, the following data will be documented or derived:

- Type of BE (spontaneous, traumatic, post-operative, joint, 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*
- Treatment details: dates and times, doses, batch numbers
- BE during inhibitor-free time period

- Frequency of BEs per patient
- Number of infusions needed to treat a BE per patient
- Study drug consumption (FVIII IU/kg BW per infusion, per BE, per month, per year) per patient
- Dose changes: increased and decreased doses of *Human-cl rhFVIII* used to treat individual BEs
  For further definition of a dose change, see below (end of this chapter)
- Dose changes: in the doses 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.
  For further definition of a dose change, see below (end of this chapter).
- Details on any concomitant medication used

* If the treatment of a BE at one bleeding 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.

Definition of dose change:
A dose change will be considered relevant if the difference in the weight adjusted doses is ≥ 30 IU/kg body weight.

*3.4.3 **Surgical Prophylaxis***

Secondary objective: To assess the efficacy of *Human-cl rhFVIII* in surgical prophylaxis

Secondary endpoints:

- Efficacy assessment of surgical prophylaxis intra-operatively (at the end of the surgery [= after last suture]) by the surgeon:

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

- Overall efficacy assessment of surgical prophylaxis taking both the intra- and post-operative assessment into account will be done by the surgeon and the haematologist at the conclusion of the post-operative phase*:

- *Excellent*: No post-operative bleeding or oozing that was not due to complications of surgery. All post-operative bleeding (due to complications of surgery) was controlled with *Human-cl rhFVIII*, as anticipated for the type of procedure.
- *Good*: No post-operative bleeding or oozing that was not due to complications of surgery. Control of post-operative bleeding due to complications of surgery required increased dosing with *Human-cl rhFVIII* or additional infusions, not originally anticipated for the type of

procedure.

- *Moderate*: Some post-operative bleeding and oozing that was not due to complications of surgery; control of post-operative bleeding required increased dosing with *Human-cl rhFVIII* or additional infusions, not originally anticipated for the type of procedure.
- *None*: Extensive uncontrolled post-operative bleeding and oozing. Control of post-operative bleeding required use of an alternate FVIII concentrate.

* For a definition see below.

For treatments and evaluations related to surgeries three phases will be considered:

- Pre-operative: any dose administered or sample drawn until 3 hours before start of surgery
- Intra-operative: any dose administered or sample drawn during surgery
- Post-operative: any dose administered or sample drawn after the end of the surgery (end of surgery is defined as "last suture") until ≥ 2 (minor surgeries) or ≥ 6 days post-surgery (major surgeries), until healing is complete and the subject returned to his regular treatment.

For all surgical procedures performed during the trial, the following data will be collected:

- Location (site) and type (planned or emergency) of surgery
- Severity of surgery (minor or major)
- Expected duration of surgical procedure
- Actual BW prior surgery (kg)
- Actual duration of surgical procedure (start and end times, i.e. skin to skin)
- Pre-, intra-, and post-operative FVIII plasma levels: FVIII:C determined by central lab (CHR and OS assay) and local lab (local standard method) within 30 min before and after each administration (pre-, intra- and postoperative), where in case of intra-operative administration this is only mandatory for major surgeries and in case of post-operative doses this is only mandatory for the first 3 doses after a major surgery
- Average and maximal expected blood loss for the planned surgical procedure and for the same procedure in a subject with normal haemostasis and of the same sex, age, and stature
- Blood loss (mL) estimation: Average expected, maximal expected and actual
- Any wound haematomas and whether they require surgical evacuation
- Laboratory tests: haematology and clinical chemistry before and 24h after end of surgery
- Vital signs (pre-, intra- and postoperatively)
- Details on concomitantly administered products including any blood/blood product transfusions but excluding drugs given for routine anaesthesia
- Details of administered dose(s) of *Human-cl rhFVIII* given pre-, intra- and/or post-operatively, including dates, times, and batch number.
- Brief narratives describing the outcome and efficacy of the interventions

*3.4.4 **Resource use***

Further objective: To examine the resource use of patients treated with *Human-cl rhFVIII*

The following parameters will be basis of a resource use analysis:

- Use of FVIII concentrates:
  Prophylaxis or on-demand, dose per kg body weight, the frequency of injection, duration of treatment, any change in treatment regimen.
- Bleeding episodes: location, severity and duration.
- Inhibitor status, any change in FVIII use, use of other haemostatic agents, hospitalisation (including ward type) and its duration.
- ITI: ITI regimen details (regimen type, FVIII use, dose per kg body weight, the frequency of injection, duration, other haemostatic agents, patients' inhibitor levels).
- CVAD (Central Venous Access Device): CVAD type, hospitalization (including ward type) and duration, surgical procedures, complications due to CVAD use and management of the complication.
- Surgery prophylaxis: dosage and duration of treatment with FVIII for surgery prophylaxis including details on the type of surgery.

The aforementioned resource parameters are collected as part of primary and secondary end points within the study. The same data will also be used to analyse resource use

In addition non-medical resource use data regarding employment, household tasks and 'care' time for caregivers will be collected in the diary.

The analysis of non-medical resource use data and further analysis of medical resource use data beyond the planned clinical analysis is not the objective of this analysis plan.

3.4.5 Determination of FVIII:C Levels

Central lab data:

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

- The chromogenic (CHR) assay and the
- One-stage (OS) assay

All recovery calculations will be based on data from either assay; the chromogenic assay is however regarded as the more advanced method yielding the more accurate results.

Routine lab data:

For ITI patients' routine lab data will be used to determine criteria for successful treatment (recovery, half-lives). These data will usually be generated from routine labs and diverse assays.

3.4.6 Actual and Labelled Potencies

For all batches of *Human-cl rhFVIII,* the actual potencies, i.e. the content of FVIII expressed as IU, are provided by the central laboratory; these data will be provided to the statistician in order to be available for the analysis. The actual potencies will be determined using both assay methods, CHR and OS, and used accordingly for calculations based on each assay. Should the central laboratory 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 recovery for non-ITI patients will be based on the actual potency whereas dosing will be based on the labelled potency.

*3.4.7 **Incremental Recovery***

Investigations of incremental recovery (optional) can be done with the first *Human-cl rhFVIII* administration (40 IU FVIII/kg BW, labelled potency), or within the first three months after treatment start with *Human-cl rhFVIII*, but in either case in a non-bleeding patient. They are recommended being controlled every 6 months thereafter. At these visits, blood samples for the calculation of the incremental recovery will be taken before study drug injection and 0.25, and 1 hours after end of injection.

*3.4.8 **Other non-routine laboratory data***

The following non-routine laboratory data will be collected. However, the details on variables supplied by central laboratories are not yet known at the time point of creation of this version of the analysis plan:

- Immunogenotyping: F8 gene mutation analysis (mandatory), categorization in null/non-null and high/low risk mutation, HLA-typing, immune response gene profiling, F8 ethnic haplotype determination (optional), (EDTA blood)

The following data generated in the study will not be analysed under this SAP:

- RNA expression analysis (optional) (whole blood, RNAse-free conditions)

- *In vitro* immunogenicity of FVIII products (optional) (citrated blood)

*3.4.9 **Clinical Safety***

Clinical safety and tolerability will be assessed by monitoring vital signs, adverse events and laboratory parameters, including inhibitors against FVIII:

- Vital signs (blood pressure, heart rate, respiratory rate, body temperature) will be assessed at the following time-points:
  - at screening,
  - before and – in case IMP was injected – 30-60 minutes after the end of the infusion at the 3-monthly visits,
  - before and – in case IMP was injected – 30-60 minutes after the end of the infusion at the completion visit.
  - With respect to surgical procedures vital signs will be recorded before, during and on the first postoperative day.
- Physical examination
  - at screening,
  - once every 6 months and
  - at study completion.
- Adverse Events will be monitored throughout the whole study period and the following data will be collected:
  - Reported term
  - Associated MedDRA terms (Low Level Term, Preferred Term, System Organ Class)
  - Date of onset
  - Severity (mild, moderate or severe)
  - Seriousness (non-serious or serious)
  - 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, drug therapy (other than IMP) started, test performed, other (to be specified)) and on study drug (none, drug withdrawn, dose reduced, dose increased)

- The safety lab panel consists of the following measurements:

  - Haematology: red blood cell count (RBC), white blood cell count (WBC), haemoglobin (HB), hematocrit (HCT), and platelet count.
  - Clinical chemistry: alanine amino transferase (ALAT), aspartate transaminase (ASAT), serum creatinine (CREA).

  The time-points for sampling for these lab parameters are:

	Screening	3-monthly visits (± 2 weeks)	Surgery (pre- and post surgery)
Haematology	✓	✓	✓
Chemistry	✓	✓	✓

4 STUDY DESIGN

4.1 General Design and Plan

This study is a prospective, open-label, multi-national, multi-center phase III study in previously untreated patients with severe Haemophilia A.

For each patient, the exposure to *Human-cl rhFVIII*, the efficacy of *Human-cl rhFVIII* in the prevention and the treatment of bleeds, the frequency of break-through bleeds in case of prophylactic treatment, the efficacy in surgical prophylaxis, and the overall safety and tolerability of *Human-cl rhFVIII* will be assessed. In the course of the follow-up visits (i.e. every 3-4 EDs until ED 20, then every 10-12 EDs until ED 100), scheduled to be performed after the Screening Visit, FVIII inhibitor levels will be assessed for each patient.
A patient completes the study by reaching 100 EDs, or after a maximum study participation period of 5 years from screening. In patients who develop FVIII inhibitors and start ITI (Immune tolerance induction; high doses of FVIII) treatment, the maximum length of ITI will be 36 months. In patients undergoing surgical interventions, treatment details will be documented for the pre-, intra-, and post-operative phase, respectively.

4.2 Sample Size

100 evaluable previously untreated patients (PUPs) will be enrolled in this study.

No inferential analysis involving formal testing is planned in this non-controlled study. Consequently, no formal sample size estimation was performed, but the sample size was chosen to satisfy CHMP recommendations.

According to the CHMP "Guideline on the Clinical Investigation of Recombinant and Human Plasma-Derived Factor VIII Products" (EMA/CHMP/BPWP/144533/2009) [1], a minimum of 50 PUPs evaluated for efficacy and safety during at least 50 EDs, connected with a post-approval commitment to follow up at least 100 PUPs (50 from efficacy/safety trial and 50 new) for a minimum of 100 ED, is necessary.

4.3 Randomization and Blinding

Not applicable.

4.4 Study Assessments

For assessments directly related to the evaluation of the primary and secondary endpoints, please refer to section 3.4 (Assessment of Objectives).

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:

- Subject demographics and baseline characteristics:
  including ethnicity, age, height, weight, family history of haemophilia and inhibitors against FVIII.
- F8 gene mutation analysis including null/non-null specification
- Immunogenotyping
  (HLA-typing, immune response gene profiling, F8 ethnic haplotype determination)
- RNA expression analysis
- FVIII level and recovery determination
- Half-life determination for patients under ITI treatment

- Medical History
- Concomitant Medication will be recorded throughout the trial
- Physical examinations will be performed at screening, at six monthly visits and at the completion visit.

5 STUDY POPULATIONS

5.1 Subject Disposition

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

- Safety analysis population: All subjects who received at least one dose of *Human-cl rhFVIII*
- Intent to Treat (ITT) analysis population: All subjects in the safety analysis population for whom any data was collected post treatment with *Human-cl rhFVIII*

  Subpopulations of the ITT population will be
  - Subjects of each ethnic group
  - Subjects with ITI treatment
  - Subjects with breakthrough bleedings, if appropriate
  - Subjects with surgical interventions, if appropriate
  - Subpopulations especially for inhibitor incidence analysis:
    - Subjects with different F8 gene mutations
    - Subjects with/without family history of inhibitors
    - Subjects by classes of EDs prior to inhibitor generation (1-5, 6-10, 11-20, 21-50, > 50)
    - Subject's age at first exposure (< 1, 1-6, > 6-12, > 12 months)
  - Subjects by reason for treatment prior to inhibitor generation
  - Subjects by intensity of treatment with/without peak treatment moments before inhibitor appearance (peak treatment moments defined as
    - ≥3 subsequent days with FVIII dosing, and/or
    - at least one day with prophylactic doses of > 50 IU FVIII /kg BW)
  - ED50 sub-population: Patients in the ITT population with at least 50 EDs of treatment with *Human-cl rhFVIII*
  - ED20 sub-population: Patients in the ITT population with at least 20 EDs of treatment with *Human-cl rhFVIII*.

- Efficacy: Per Protocol (PP) analysis population: All subjects in the ITT analysis population who completed the trial without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the efficacy results.

  Especially the following subjects will be excluded from this population:
  - Subjects who violate the following inclusion criteria:
    - severe haemophilia A (FVIII:C < 1%; historical value as documented in subject records),
    - no previous treatment with FVIII concentrate or other blood products containing FVIII
  - Subjects who fulfil at least one of the following exclusion criteria:
    - other coagulation disorder than haemophilia A
    - severe liver or kidney disease (ALT and AST levels >5 times of upper limit of normal, creatinine >120 µmol/L),
    - concomitant treatment with any systemic immunosuppressive drug,
  - Subjects who use concomitant medication that may confound study results, like e.g. alpha-interferon or prednisone
  - Subjects with 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.

- Subjects with dosing or treatment errors like e.g. the use of other FVIII products (except for emergencies) or several *unexplained* and significant deviations from the recommended dose regimen.
- Subjects for whom less than a minimum of inhibitor tests is available*
- Patients with less than 95 days of exposure to *Human-cl rhFVIII*.

*Defined during Data Review Meeting for the interim analysis on April 7, 2016:
if less than 1 inhibitor test is available for any of the following periods:
- baseline, if first result of inhibitor screening after first exposure to the study drug is positive (it cannot be assured that the patient is a PUP),
- between ED2 and ED20,
- between ED21 and ED50.

- Population of subjects on prophylactic treatment schedule (PROPH): All subjects in the ITT population who have at least one prophylactic treatment. Only data under prophylaxis will be used for the analyses.

- Per-protocol population of subjects on prophylactic treatment schedules (PROPH-PP): All subjects in the PP population who have at least 95 EDs of treatment and who have no significant dosing or treatment errors, like e.g. unexplained interruptions of the prophylaxis with *Human-cl rhFVIII*.

- Population of subjects on continuous prophylaxis (PROPHcont): All subjects in the ITT population who have at least one prophylactic treatment and have been assigned to the subgroup of patients receiving continuous prophylaxis, i.e. prophylactic treatment period of at least 169 calendar days, and have not received a mixture of on-demand and prophylactic treatment (however, subjects who were treated on-demand only once and switched to prophylactic treatment thereafter, will be kept in this population).

- Population of subjects with on-demand treatment (OD): All subjects in the ITT population with at least one period of on-demand treatment. Only data under on-demand treatment will be used for the analyses.
  (Definition of period under OD: A patient in the main study is defined to be under prophylaxis during all time periods within 14 days after each prophylactic treatment. A patient in the main study is defined to be under OD in time periods he is not under "Prophylaxis" according to previous definition)

- Population of BEs (BLEED): All documented treated BEs of subjects in the ITT population for which
  - any amount of treatment with *Human-cl rhFVIII* is documented
  (either the treatment is indicated with reason "Bleeding" or ITI treatment and an efficacy assessment for the BE is documented).
  - start between first BE treated with *Human-cl rhFVIII* and the completion visit
  Note: Any type of BE is included: spontaneous, traumatic, post-operative or other

  Additional to version 2.0 of the SAP, part of the analysis will be restricted to BEs during inhibitor-free periods.

- Population of BEs per protocol (BLEED-PP): All documented bleeds in the BLEED population of subjects in the PP population, which
  - are *not* treated with another FVIII or bypassing agents
  Note: Any type of BE is included: spontaneous, traumatic, post-operative or other

  Additional to version 2.0 of the SAP, part of the analysis will be restricted to BEs during inhibitor-free periods.

- Surgery population (SURG): All documented surgical interventions of subjects in the ITT population for which
  - any amount of *Human-cl rhFVIII* prior to, during or after the surgery is documented and
  - no other FVIII concentrate is documented within 24 hours prior to surgery*.

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

  *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.

  Additional to version 2.0 of the SAP, part of the analysis will be restricted to surgeries during inhibitor-free periods.

- Infusions analysis population (Safety-INF): All documented infusions with *Human-cl rhFVIII* to subjects of the Safety population.
  For the definition of temporally associated AEs: AEs will be related to a subject's infusion No. i, if the AE starts during infusion No. i or within 24 hours after infusion No. i, but before the same subject's infusion No. i+1.

The subject disposition, i.e. the identification of significant deviations to consider for the PP population 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.

There may be further reasons to exclude patients from analysis populations without an underlying protocol deviation. This comprises:
- Patients withdrawn from study according to protocol with incomplete data.

The ITT analysis is considered to be most relevant for the analysis of immunogenicity data; the PROPH population is considered to be 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 treatment of bleeds and the SURG population is considered to be the most relevant for the analysis of efficacy data on treatment during surgeries. To evaluate the robustness of the study results, efficacy analyses will also be done based on the PP population.

5.2 Protocol Deviation Assessment

Protocol deviations will be assessed as major or minor with respect to the analysis populations defined in section 5, and listed as part of the database release procedures prior to data analysis, and will include:

- Violation of inclusion or exclusion criteria
- Concomitant medication that may confound study results (see protocol chapter 4.2.2 Forbidden Concomitant Medication)
- Non-compliance issues raised by the investigator or sponsor.
  Dosing or treatment errors like e.g. the use of other FVIII products (except for emergencies) or significant deviations from the recommended dose regimen.
- Less than a minimum of inhibitor tests (see Chapter 5.1, definition of PP population) available
- Less than 100 days of exposure to *Human-cl rhFVIII* at completion (< 95 EDs is regarded as major, 95-99 EDs is regarded as minor protocol deviation; if an inhibitor is detected prior to 95 EDs and the patient switched to ITI treatment, this is not regarded as a protocol deviation)

A list of major protocol violations will also be included in the Clinical Study Report.

6 STATISTICAL ANALYSIS

Please refer to section 13 for an overview of tables (marked "T"), listings ("L") and figures ("F").

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 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.
  In addition this type of data can be shown in life-tables.

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.

Please refer to section 13 for a table of tables included in the statistical report.

6.2 Figures

Figures will always reference to 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 ± standard deviation over time points will be used to illustrate the statistical outcome. Please refer to section 13 for a table of figures included in the statistical report.

6.3 Listings

For selected results, statistical summarization alone seems inappropriate, and listings will be presented to facilitate in-depth review of the data; these include:

- AE
- Reason for withdrawal

SAS datasets including individual subject data will be prepared. Datasets will be available on request, e.g. for an electronic submission according to CDISC /SDTM. Therefore no listings will be prepared for Section 16.4. Please refer to section 13 for a table of listings included in the statistical report.

6.4 Statistical Analytical Issues

The statistical analysis of the primary, secondary and safety endpoints is to be understood in the exploratory sense. Therefore no confirmative statistical analysis is planned.

6.4.1 Adjustments for Covariates

Not applicable.

6.4.2 Handling of Dropouts or Missing Data

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

- Body weight: In case of missing weight, the last available weight measurement will be used (last observation carried forward). Body weight will be estimated for the first exposure day: if body weight is not available on ED1 it will be estimated by linear interpolation between last available data before and after ED1.
- Date of birth: only month and year will be presented in listings.
- Age: calculations at screening and at ED1 in case of partially missing data:
  - If month and year available: "1" for day will be imputed
  - If month missing, but year available: "July" will be imputed
  - If month missing, but year available: " 1st of July" will be imputed
  - no imputation otherwise
- Inhibitor measurement in the ITI study: In case inhibitor measurements have turned from positive to negative in the ITI sub-study and are missing at subsequent determinations of recovery and/or half-lives, they will be carried forward in order to facilitate the calculation of the number of ITI success criteria.
- 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 for subjects switching to another FVIII product during their study participation, and will thus **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 either of these 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 all haemostatic efficacy assessment after the switch 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.*

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 terms of both, total days and exposure days.

6.4.3 Interim Analyses and Data Monitoring

One interim analysis was conducted.

The interim analysis comprised the complete analysis as planned for the final analysis, except for the Health economic modeling analysis, the resource use data, RNA expression and Epitope mapping data, and the PK analyses for patients receiving ITI. All analyses were based on available data at that time.

Time-Point of Analysis

Interim analysis: once 50 patients achieved at least 50 EDs.

For the interim analysis the data to be analysed was frozen in a data snapshot for the analysis.

The final statistical analysis was conducted upon successful completion of all database release (DBR) procedures and sign-off of the DBR release form.

6.4.4 Multicentre Studies

No analysis on between centre effects is planned.

6.4.5 Multiple Comparisons/Multiplicity

Not applicable.

6.4.6 Use of an 'Efficacy Subset' of Subjects

For each efficacy analysis primarily analysed by the intention-to-treat principle, an additional per-protocol set will be defined (See Sections 5.1) for which the most important efficacy analyses will be repeated as a secondary analysis.

6.4.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

6.4.8 Examination of Subgroups

Part of the analyses will be performed in sub-groups defined in Chapter 5.1.

For the combined presentation of subgroup results, Forest plots will be provided.

7 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The following demographic data will be collected:

- Birth date (Age) or at least month and year, Ethnic origin; "male" will be the standard value for Sex in the CRF.
  Age will be calculated from the month and year of birth and the start of the first IMP administration.

Further baseline characteristics are:

- Height, Weight; Body Mass Index (BMI) which will be calculated from height and weight
- FVIII activity (%), FVIII antibody and Bethesda assay result (BU) (both assays) at screening
- Previous and concomitant medications
- Medical history and physical examination
- Underlying F8 gene defect including null/non-null mutation analysis (blood samples collected by the Investigator and analysis performed by a central laboratory)
- Family history of haemophilia and inhibitors against FVIII

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

8 EVALUATION OF TREATMENT COMPLIANCE AND EXPOSURE

Prophylaxis, ITI treatment and treatment of Bes and surgeries: The following will be tabulated and/or summarized:

- Reason for Administration
- Number of Injections
- First dose, last dose, number of Exposure Days
- Total Dose (IU)
- Dose (IU FVIII/kg BW)

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

9 EVALUATION OF TREATMENT EFFICACY

9.1 Immunogenicity

All recorded determinations of inhibitors against FVIII will be listed. The absolute number and cumulative incidence of inhibitors (inhibitor titre ≥ 0.6, < 5 BU and ≥ 5 BU 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, and a logistic regression analysis of incidence rates of FVIII inhibitor development will be performed (prognostic factors: family history of inhibitor, family history of hemophilia, weight, mean dose/ED, age, F8 gene mutation defect (including null/non-null, high/low risk mutation analysis), number of EDs before inhibitor development, age at first treatment, intensity of treatment (number of peak treatment moments), country ethnicity, center).
In addition, number of EDs until inhibitor development will be shown in life-table lists showing the incidence of inhibitors per interval of 5 EDs; a Cox regression will analyse the ED to inhibitor data for the impact of possible prognostic variables (same list as for logistic regression analysis above).

The incidence of low and high titre FVIII inhibitors will also be presented grouped by ethnicity and F8 gene mutations categorized as null/non-null and as high/low risk, incl. results of the immunogenotyping sub-study. For the combined presentation of subgroup results, Forest plots will be provided.

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

RNA expression analysis data and Antitope Ltd. sub-study data will not be analysed under this SAP.

9.2 Prophylaxis (Prevention of Bleeding episodes)

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

- Number of subjects treated prophylactically
- Characteristics and number of prophylactic treatments: Treatment intervals, dosage, changes or interruptions in prophylactic treatments
- Number of injections and exposure days. Injections administered over midnight will only count as exposure day on the day on which the injection had started.
- Amount of *Human-cl rhFVIII* used (per month, per year*, exposure day and injection, and in total)
  *projected estimate
- Overall efficacy assessment at the end of the study: Number and rate (per month and per year) of spontaneous BEs in subjects on prophylactic treatment*;
  in total, as well as broken down to intensity of prophylaxis, timely distance from last study drug administration, dose(s) and characteristics of BE (type, site and severity of BE).
  *The rate of BEs will exclude BEs and the time period between start of surgery-related prophylactic treatment and re-start of prophylactic treatment after surgery.
  It will also exclude BEs and time periods of "on-demand" treatment, if any.

- In two additional secondary analyses, overall efficacy analysis for prophylactic treatment will be analysed
  - for traumatic BEs
  - for all BEs (spontaneous, traumatic, others (if any)).
- Further analysis on bleeding rates will be performed in patients who developed an inhibitor, but only during their inhibitor-free periods. An inhibitor is regarded as confirmed between its'start date, as defined in Chapter 3.4.1, Definition "I4", and the time when the inhibitor titre decreases again to <0.6 BU for the first time, which has to be confirmed by a subsequent measurement of < 0.6 BU; should the inhibitor titre however not have decreased to < 0.6 BU during the study the period with confirmed inhibitor lasts until the end of the study. Periods of prophylaxis without confirmed inhibitor are regarded as "inhibitor-free".
- Study drug consumption data for prophylactic treatment (IU FVIII /kg BW per month, per year, exposure days) per subject and in total (for subjects on prophylactic treatment) will be presented descriptively.

9.3 Treatment of Breakthrough Bleeding Episodes

Additional to version 2.0 of the SAP, all analyses described below will also be done for those bleedings reported during inhibitor-free periods.

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

- Number of BEs, rates of BEs (per site and type of BE)

  Remark: If the treatment of a BE in one bleeding site is interrupted for ≥ 48 hours, the event is to be recorded as two separate BEs; if however different Type of BE (spontaneous, traumatic, post-operative, other)
- Type of FVIII treatment (prophylactic, on-demand, ITI) at start of BE
- Site of bleeding episode
- Date and time of occurrence/of noticing and of end of the bleeding episode; the duration of the BEs will be calculated and presented as well
  - Treatment duration for BE =
    End date/time – start date/time of BE;
    if end time missing: impute 23:59 of same day,
    if start time missing: impute 0:00 of same day.
- Severity of the BE (minor, moderate, major, life threatening) by type and by site of BE
- Efficacy assessment by the subject at the end of the bleeding episode, together with the investigator in case of on-site treatment (excellent, good, moderate, none)

  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" means all "excellent" and "good" efficacy ratings of treated BEs.

  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 for subjects switching to another FVIII product during their study participation which will **not** be considered treatment failures in the efficacy analyses:

a) 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)
b) if the IMP was not available for the patient in time (example: patient experiences severe BE but has not enough product available at home).

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 assessment).
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".
* Subjects will be excluded from the PP population.

- Treatment details: number of exposure days, number of injections, dosing incl. batch nos., consumption of *Human-cl rhFVIII* (IU/kg BW per month, per year, per BE)
- Frequency of BEs
- Number of infusions needed to treat a BE
- Study drug consumption (FVIII IU/kg BW per infusion, per BE, per month, per year)
- Changes: increased and decreased doses of *Human-cl rhFVIII* (IU/kg BW) used to treat individual BEs.
  For further definition of a dose change, see Chapter 3.4.2.
- Changes in the doses 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.
  For further definition of a dose change, see Chapter 3.4.2.
- Any haemostatic co-medication will be listed.

9.4 Haemostatic control in Surgical Procedures

Additional to version 2.0 of the SAP all analyses described below will also be done for those surgical procedures performed during inhibitor-free periods.

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

- Number of subjects undergoing surgeries (minor, major, total)
- Number of surgeries (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 subject with normal haemostasis and of the same sex, age, and stature, subject's body weight)
- Details on treatment for surgical prophylaxis (number of exposure days and injections 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 injections, dosing details amount of trial product)
- Characteristics and amount of other blood products or rescue medication administered at any time prior, during or post the surgical procedure
- Efficacy evaluation by the surgeon at the end of the surgery and by the surgeon and the haematologist on the last post-operative day (end of post-operative phase).

  In addition to the four point scale (very good, good, moderate, none), the proportion of surgeries with successful treatment according to the overall efficacy assessment will be presented.
  "Successfully treated" are all "excellent" and "good" efficacy ratings of surgical procedures.

  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
  * those surgeries will be excluded from the SURG-PP population.

- These patients may stay in the study until they have reached their regular end of the study
- 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
- Pre-, intra-, and post-operative FVIII plasma levels
- Any wound haematomas and whether they require surgical evacuation
- Laboratory tests: haematology and clinical chemistry (pre- and postoperatively)
- Vital signs (pre- intra- and postoperatively)
- Details on concomitantly administered products including any blood/blood product transfusions but excluding drugs given for routine anaesthesia.

9.5 On-demand treatment

Study drug consumption data for on-demand treatment (IU FVIII /kg BW per month, per year; exposure days) per subject and in total (for subjects on prophylactic treatment) will be presented descriptively for subjects receiving on-demand treatment.

9.6 ITI treatment

The percentage of subjects under ITI treatment with complete success (inhibitor-free, normalised recovery and half-life; see Chapter 10) of the therapy will be displayed descriptively. Kaplan-Meier curves will show the distribution of the time to complete success.

Study drug consumption data for subjects with ITI treatment (IU FVIII /kg BW per month, per year; exposure days) per subject and in total will be presented descriptively.

9.7 Resource Use Analysis Plan

The statistical analysis of resource use parameters will be descriptive.

Continuous characteristics (i.e. drug usage, duration of hospitalisation, days lost at work, etc.) will be described in terms of mean/median/ standard deviation and range). Dichotomous or categorical variables (i.e. number of hospitalizations, CVAD use, etc.) will be described by frequency tables and percentages.

- Use of FVIII concentrates:
  - Prophylaxis or on-demand,
  - dose per kg body weight separated for prophylaxis and on-demand,
  - the frequency of injection separated for prophylaxis and on-demand,
  - duration of treatment separated for prophylaxis and on-demand,
  - any change in treatment regimen separated for prophylaxis and on-demand,
  - duration of FVIII treatment separated for prophylaxis and on-demand.
  - use of other haemostatic agents separated for prophylaxis and on-demand
  - number and time of hospitalizations (including ward type) separated for prophylaxis and on-demand
- Inhibitor status
  - any change in FVIII use when changing from negative to positive and vice versa,
  - use of other haemostatic agents separated for with and without inhibitor,
  - number and duration of hospitalization (including ward type) separated for with and without inhibitor.
- Bleeding episodes: location, severity and duration
  Listings will indicate whether subjects were under prophylaxis, under on-demand or under ITI therapy and whether they had a positive inhibitor or not at the time of the BE.
- ITI: ITI regimen details (regimen type, FVIII use, dose per kg body weight, the frequency of injection, duration, other haemostatic agents, patients' inhibitor levels.
- CVAD (Central Venous Access Device):
  - CVAD type,
  - number and duration of hospitalizations (including ward type),
  - number and type of surgical procedures,
  - complications (adverse events) due to CVAD use and management of the complication (text variable), separated for with and without inhibitor.
- Surgery prophylaxis: dosage and duration of treatment with FVIII for surgery prophylaxis including details on the type of surgery
  Listings will indicate whether or not the patient had a positive inhibitor at the time of the surgery.

Health economic modeling analysis with resource use parameters is planned at study closure; this part of the analysis is not objective of this analysis plan.

10 PHARMAKOKINETICS AND EVALUATION OF RECOVERY

The incremental recovery of *Human-cl rhFVIII* can optionally be determined with the first *Human-cl rhFVIII* administration or within the first three months after treatment start with *Human-cl rhFVIII*. It is recommended to be controlled every 6 months.

Blood samples for the calculation of the incremental recovery will be taken before study drug injection and after 0.25 and 1 hour post-infusion.

FVIII:C values below the limit of quantification will be set to 0 for recovery calculations.

In-vivo incremental recovery will be calculated in the following way with both assays (chromogenic (CHR) and one-stage (OS) assay):

Recovery (according to assay a) (In vivo incremental recovery)	will be determined from the FVIII level before ($C_{pre,a}$) and the peak level after ($C_{max,a}$) the injection of *Human-cl rhFVIII* : $\text{Re}\, c_a = \frac{(C_{\max,a} - C_{pr,a}) \cdot BW}{D_a}$ where BW stands for the body weight in kg and D_a is the dose according to the actual potency of the FVIII concentrate as described in [1] below

[1] The actual dose D_a based on the real potency of the batch of *Human-cl rhFVIII* used will be calculated as $D_a = D_{nom} * \frac{ActualPotency(a)}{LabeledPotency}$ where D_{nom} stands for the nominal Dose according to the product label and a stands for the respective assay: chromogenic assay or one-stage assay.

Summary statistics per time point will be prepared for the recovery, including mean and standard deviation, median, range, geometric mean and the associated geometric standard deviation and confidence intervals.

Intra-subject variability over different recovery measurements will be shown graphically in recovery profiles.

Plots showing mean ± standard deviation of the factor VIII concentrations per assay and per nominal time point will be presented.

In the course of ITI treatment, recovery will be determined after inhibitor elimination to test if the recovery is at least 66% of normal (defined as 1 IU FVIII/kg BW raises the plasma FVIII activity by 1.5%).

Half-life calculation for patients on ITI

Available PK data for half-life determination of *Human-cl rhFVIII* in patients on ITI will be calculated. In the course of ITI treatment it will be tested, if the half-life is at least 6 hours.

T_{max}	Time when C_{max} is observed	Timing starts at end of injection
$T_{1/2}$	Elimination half-life	using linear regression on the terminal phase* of the logarithm of the concentration; $T_{1/2} = \frac{\ln(2)}{K}$ (where *K,* the elimination rate constant, is determined as the slope of the regression line)

*The non-compartmental approach does not presume that the plasma concentration follows a mono-exponential decay during the complete elimination phase ($t \geq T_{max}$). The appropriate time point when the terminal elimination phase starts will be determined automatically by the Software WinNonlin using the algorithm described in APPENDIX I: DETERMINATION OF SLOPE OF ELIMINATION CURVE BY NON-COMPARTMENTAL PK ANALYSIS WITH WINNONLIN® [[2] , Chapter 9, pages 218-219]. In addition visual examinations on the choice of the software will be performed on individual plots of the natural logarithm of the plasma levels *ln(C)* (CHR and OS)

Half-lives and recovery determinations in ITI patients will be listed and used for the assessment of complete success of an ITI treatment.

10.1 Complete success of ITI therapy

Complete success of a patient's ITI will be defined as:

- FVIII:C inhibitor negative (<0.6 BU) (at two sequential measurements)

- Recovery ≥ 0.99 %/(IU/kg BW) (= 66% of 1.5 %(IU/kg BW))

- terminal half-life ≥ 6 hours

Complete success is
1) documented in the "ITI Study Completion" by the investigator and
2) derived from the documented data on the objective criteria
   - in the inhibitor data
   - as derived from the recovery/half-life data
     (central and/or local lab determinations with one-stage assay and/or chromogenic assay)

If more than one lab determination is available (e.g. local and central lab; several assays), worst available values are taken into account for the inhibitor criterion (highest titre) and the recovery criterion (lowest IVR); this also applies for the half-life criterion (lowest half-life). However, there may be exceptions when there is a difference in available data for PK analysis and one of the series of measurements is expected to provide more reliable estimations of the terminal half-life data than the other(s); if necessary, reliability of series of measurements in terms of available data for PK analysis will be assessed in data review meetings before interim and final analysis.

11 EVALUATION OF SAFETY PARAMETERS

11.1 Adverse Events

All adverse events occurring or worsening after initiation of study treatments until the completion visit (treatment emergent AEs) will be displayed in summary tables and listings.

Incidences of adverse events will be given as numbers and percentages of subjects; 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 15.0 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 trial drug (by MedDRA System Organ Class (SOC)/ preferred term)
- Any AE temporally related (within 24 hours after end of infusion*) to the trial drug (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 (Adverse drop-out)

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

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 counts, prior exposure days to *Human-cl rhFVIII* and total amount of *Human-cl rhFVIII* used prior to the AE to evaluate the need of further investigation of any apparent pattern or trend in AE rates.

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

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

- Subject identifier and characteristics (age, 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 (other than IMP) started, tests performed, other (to be specified)) and on study drug (none, product withdrawn, dose reduced, dose increased)
- Outcome (recovered, recovering, not recovered, recovered with sequelae, fatal, unknown)
- Causality assessment (probable, possible, unlikely, not related)
- Study treatment 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)

11.2 Laboratory Data

Routine laboratory parameters will be listed for all subjects, 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 statistics on the changes from baseline (i.e. Screening for fixed times of schedule, and before surgery for surgeries) will be provided. A brief statement will be included in the CSR to highlight noticeably outliers or patterns.

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

11.3 Vital Signs

Blood pressure (systolic/diastolic), heart rate, respiratory rate and body temperature will be tabulated, and the sample characteristics will be presented by time point. In addition statistics on the changes from baseline (i.e. Screening for fixed times of schedule, and before surgery for surgeries) will be provided.

11.4 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.

11.5 Concomitant Medications

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 15.0 or later)).

12 REFERENCES

[1] Guideline on the Clinical Investigation of Recombinant and Human Plasma-derived Factor Products" (EMEA/CHMP/BPWP/144533/2009, London, 21 July 2011).

[2] Pharsight: WinNonlin User's Guide, part 1, Version 4.1, 1998-2003 Pharsight Corporation.

13 TABLES, FIGURES AND LISTINGS REFERRED TO BUT NOT INCLUDED IN THE TEXT OF THE CSR (SECTION 14 AND 16.2 OF THE CSR)

The following tables, figures and lists will be generated.

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 of y'.

The order and numbering of the various parts of the Clinical Study Report 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 subjects/ events in this population (N) and the number of subjects/events actually contributing to the particular output (n).

14		*Tables, figures and listings referred to but not included in the text of the CSR (section 14 of the CSR)*	
14.1.1.1	T	*Subject Disposition and analysis populations* *number of subjects enrolled, erroneously enrolled, treated, completed, prematurely discontinued*	All
14.1.1.2	T	*Bleeding episodes analysis populations*	BLEED
14.1.1.3	T	*Surgery analysis populations*	SURG
14.1.2.1-3	T	*Protocol Deviations* *Frequency of protocol violations by "minor" and "major" and in total* *(3 sub-tables: for minor, major, total)*	SAF
		Demographic Data Summary figures and tables	
14.1.3	T	*Number of subjects per center and analysis population*	SAF
14.1.4	T	*Statistics on age, body height, body weight, body mass index, ethnicity and blood type*	All
14.1.4.1	T	*Statistics on age, body height, body weight, body mass index, ethnicity and blood type – in ED20 sub-population*	All
14.1.4.1.1	T	*Statistics on age, body height, body weight, body mass index, ethnicity and blood type – patients with confirmed inhibitors in ED20 sub-population*	All
14.1.4.2	T	*Statistics on age, body height, body weight, body mass index, ethnicity and blood type – in ED50 sub-population*	All
14.1.4.2.1	T	*Statistics on age, body height, body weight, body mass index, ethnicity and blood type – patients with confirmed inhibitors in ED50 sub-population*	All
14.1.5	T	*Statistics on study participation (first- and last treatment, duration of treatment, EDs)*	All
14.1.6	T	*Underlying gene defects (F8 gene analysis)* *(including categorization for null/non-null mutations, high risk/low risk mutations)*	All
14.1.7	T	*Family history of haemophilia and/or inhibitors against FVIII*	All
14.1.7.1	T	*Family history of haemophilia and/or inhibitors against FVIII - in ED20 sub-population*	All
14.1.7.1.1	T	*Family history of haemophilia and/or inhibitors against FVIII - patients with confirmed inhibitors in ED20 sub-population*	All
14.1.7.2	T	*Family history of haemophilia and/or inhibitors against FVIII - in ED50 sub-population*	All
14.1.7.2.1	T	*Family history of haemophilia and/or inhibitors against FVIII - patients with confirmed inhibitors in ED50 sub-population*	All
14.1.8	T	*FVIII activity (%) and Bethesda assay results (BU) at screening*	All
14.1.9.1-2	T	*Frequency of use of prior and concomitant medications by ATC class (without surgeries)* *(2 sub-tables: 1 for prior, 1 for concomitant)*	ITT, SAF
		IMMUNOGENICITY	
14.2.1.1	T	*Statistics on incidence of inhibitors (≥0.6, <5 and ≥5 BU) incl. 95% confidence interval - overall and per subgroups: age at first treatment, race, family history, F8 gene mutation defect, null/non-null mutation, high risk/low risk mutations, mean dose/ED, number of EDs before inhibitor development, reason and intensity of treatment subgroup*	ITT, PP
14.2.1.2	T	*Statistics on incidence of inhibitors (>=0.6, <5 and >=5 BU) incl 95% confidence interval - per ED20 subgroups and ED50 subgroups*	ITT, PP

14.2.1.3	T	*Statistics on peak inhibitor titres*	ITT, PP
14.2.2.1	T	*Statistics on time from ED1 to first confirmed inhibitor activity in patients with any inhibitors by intensity of treatment*	ITT, PP
14.2.2.2	T	*Statistics on the number of EDs before first confirmed inhibitor activity in patients with any inhibitors by intensity of treatment*	ITT, PP
14.2.2.3	T	*Statistics on the number of EDs before confirmed first inhibitor activity in patients with high titre inhibitors by intensity of treatment*	ITT, PP
14.2.2.4	T	*Statistics on the number of EDs before first confirmed inhibitor activity in patients with low titre inhibitors by intensity of treatment*	ITT, PP
14.2.2.5	T	*Statistics on the number of EDs before first inhibitor activity in patients with any inhibitors – by reason of treatment (on-demand, prophylaxis, combinations)*	ITT, PP
14.2.2.6	T	*Statistics on the number of EDs before first inhibitor activity in patients with only high titre inhibitors (on-demand, prophylaxis, combinations)*	ITT, PP
14.2.2.7	T	*Statistics on the number of EDs before first inhibitor activity in patients with only low titre inhibitors- by reason of treatment (on-demand, prophylaxis, combinations)*	ITT, PP
14.2.3.1-3	F	*Kaplan-Meier curves on number of EDs until first inhibitor activity (any inhibitor, high titre inhibitor, low titre inhibitor,)*	ITT, PP
14.2.3.4-6	T	*Kaplan-Meier curves on number of EDs until first confirmed inhibitor activity – Display of product limit estimates (any inhibitor, low titre inhibitor, high titre inhibitor)*	ITT, PP
14.2.4.1-3	F	*Kaplan-Meier curves on number of EDs until first inhibitor activity by F8 mutation type, null and non-null mutation (any inhibitor, high titre inhibitor, low titer inhibitor)*	ITT, PP
14.2.4.4-6	T	*Kaplan-Meier curves on number of EDs until first inhibitor activity by F8 mutation type, null and non-null mutation (any inhibitor, high titre inhibitor, low titer inhibitor) – Display of product limit estimates*	ITT, PP
14.2.4.7-9	T	*Life-tables : Risk of inhibitor incidence over time in steps of 5 EDs (any inhibitor, high titre inhibitor, low titer inhibitor) – Display of life-table estimates*	ITT, PP
14.2.5	T	*Logistic regression analysis for any, low- and high-titre inhibitors (prognostic factors: family history of hemophilia, family history of inhibitors, weight, mean dose/ED, age, F8 gene mutation defect, null/non-null mutation, number of EDs before inhibitor development, age at first treatment, intensity of treatment, country, center, ethnicity)*	ITT, PP
14.2.6	T	*Cox regression analysis for any, low- and high-titre inhibitors (initial model with same prognostic variables like in 14.2.5)*	ITT, PP
14.2.7	T	*Statistics on the number of exposure days and injections administered for ITI treatment with Human-cl rhFVIII*	ITI
14.2.8	T	*Statistics on the amount of Human-cl rhFVIII (IU) for ITI treatment per month, per year, per exposure day, per injection and in total*	ITI
14.2.9	T	*Statistics on the dosage of Human-cl rhFVIII (IU/kg) for ITI treatment per month, per year, per exposure day, per injection and in total*	ITI
14.2.10	T	*ITI: Statistics on changes in treatment schedule*	ITI
14.2.11	T	*ITI: Frequency table on haemostatic agents used under ITI*	ITI
14.2.12	T	*ITI: Frequency table on number and percentage of finalized ITI therapy (Number of criteria fulfilled and rate of complete successes)*	ITI
14.2.13	T	*ITI: Frequency table on number and percentage of individual criteria of success fulfilled*	ITI
14.2.14	F	*ITI: Kaplan Meier curves on time to complete success (any inhibitor, low titre inhibitor, high titre inhibitor)*	ITI
		PROPHYLAXIS	
14.2.15	T	*Number of exposure days and number of infusions administered for prophylactic treatment with Human-cl rhFVIII*	PROPH, PROPH-PP
14.2.16.1	T	*Statistics on the number of exposure days for prophylactic treatment to Human-cl rhFVIII and number of dosages administered*	PROPH, PROPH-PP
14.2.16.2	T	*Statistics on the number of exposure days for prophylactic treatment to Human-cl rhFVIII and number of dosages administered - restricted to subjects assessed to have received continuous prophylaxis*	PROPHcont
14.2.17.1	T	*Statistics on the amount of Human-cl rhFVIII (IU) for prophylactic treatment per month, per year, per exposure day, per injection and in total*	PROPH, PROPH-PP
14.2.17.2.1	T	*Statistics on the dosage of Human-cl rhFVIII (IU/kg)) for prophylactic treatment per month, per year, per exposure day, per injection and in total*	PROPH, PROPH-PP

14.2.17.2.2	T	*Statistics on the amount of Human-cl rhFVIII (IU/kg) for prophylactic treatment per month, per year, per exposure day, per injection and in total - restricted to subjects assessed to have received continuous prophylaxis*	PROPHcont
14.2.17.2.3	T	*Statistics on the amount of Human-cl rhFVIII (IU/kg) for prophylactic treatment during the inhibitor-free period per month, per year, per exposure day, per injection and in total - restricted to subjects assessed to have received continuous prophylaxis*	PROPHcont
14.2.18.1	T	*Prophylactic Treatment (dose changes and interruptions of prophylactic treatment)*	PROPH, PROPH-PP
14.2.18.2	T	*Prophylactic Treatment: Frequency table on haemostatic agents used under prophylactic treatment*	PROPH, PROPH-PP
14.2.19.1.1 .1	T	*Overall Efficacy Assessment of Prophylactic Treatment (Rate of BEs with 95% confidence interval) – Spontaneous BEs*	PROPH, PROPH-PP
14.2.19.1.1 .2	T	*Overall Efficacy Assessment of Prophylactic Treatment (Rate of BEs with 95% confidence interval) – spontaneous BEs – only patients on continuous prophylaxis*	PROPHcont
14.2.19.1.2 -6	T	*Overall Efficacy Assessment of Prophylactic Treatment (Rate of BEs with 95% confidence interval)– spontaneous BEs – by subgroup* *(5 sub-tables for each sub-group: site of BE, severity of BE, timely distance from last study drug administration, intensity of prophylaxis, by joint / non-joint bleedings)*	PROPH, PROPH-PP
14.2.19.1.7	T	*Overall Efficacy Assessment of Prophylactic Treatment (Rate of BEs with 95% confidence interval) – spontaneous BEs – only patients on continuous prophylaxis by joint / non-joint bleedings*	PROPHcont
14.2.19.2.1 .1	T	*Overall Efficacy Assessment of Prophylactic Treatment (Rate of BEs with 95% confidence interval) – Traumatic BEs*	PROPH, PROPH-PP
14.2.19.2.1 .2	T	*Overall Efficacy Assessment of Prophylactic Treatment (Rate of BEs with 95% confidence interval) – Traumatic BEs – only patients on continuous prophylaxis*	PROPHcont
14.2.19.2.2 -6	T	*Overall Efficacy Assessment of Prophylactic Treatment (Rate of BEs with 95% confidence interval) – Traumatic BEs – by subgroup* *(5 sub-tables for each sub-group: site of BE, severity of BE, timely distance from last study drug administration, intensity of prophylaxis, by joint / non-joint bleedings)*	PROPH, PROPH-PP
14.2.19.2.7	T	*Overall Efficacy Assessment of Prophylactic Treatment (Rate of BEs with 95% confidence interval) – Traumatic BEs – only patients on continuous prophylaxis - by joint / non-joint bleedings*	PROPHcont
14.2.19.3.1 .1	T	*Overall Efficacy Assessment of Prophylactic Treatment (Rate of BEs with 95% confidence interval) – all types of BEs*	PROPH, PROPH-PP
14.2.19.3.1 .2	T	*Overall Efficacy Assessment of Prophylactic Treatment (Rate of BEs with 95% confidence interval) – all types of BEs – only patients on continuous prophylaxis*	PROPHcont
14.2.19.3.2 -6	T	*Overall Efficacy Assessment of Prophylactic Treatment (Rate of BEs with 95% confidence interval) – all types of BEs - by subgroup* *(5 sub-tables for each sub-group: site of BE, severity of BE, timely distance from last study drug administration, intensity of prophylaxis, by joint / non-joint bleedings)*	PROPH, PROPH-PP
14.2.19.3.7	T	*Overall Efficacy Assessment of Prophylactic Treatment (Rate of BEs with 95% confidence interval) – all types of Bes – only patients on continuous prophylaxis - by joint / non-joint bleedings*	PROPHcont
14.2.19.4.1 .1 - 14.2.19.6.7	T	*Overall Efficacy Assessment of Prophylactic Treatment... (like 14.2.19.1.1-14.2.19.3.7) – during inhibitor-free periods*	PROPH, PROPH-PP
14.2.19.6.8 .1	T	*Overall Efficacy Assessment of Prophylactic Treatment (Rate of BEs with 95% confidence interval) - Spontaneous BEs - during time with confirmed inhibitor*	PROPH, PROPHPP
14.2.19.6.8 .2	T	*Overall Efficacy Assessment of Prophylactic Treatment (Rate of BEs with 95% confidence interval) - Traumatic BEs - during time with confirmed inhibitor*	PROPH, PROPHPP
14.2.19.8.3	T	*Overall Efficacy Assessment of Prophylactic Treatment (Rate of BEs with 95% confidence interval) - all types of BEs - during time with confirmed inhibitor*	PROPH, PROPHPP
14.2.19.7.1		*Annualized bleeding rates based on Poisson distribution - Prophylactic treatment*	PROPH, PROPHPP
14.2.19.7.2		*Annualized bleeding rates based on Poisson distribution - Prophylactic treatment – during inhibitor-free periods*	PROPH, PROPHPP
14.2.19.7.3		*Annualized bleeding rates based on Poisson distribution - Prophylactic treatment – during inhibitor-free periods – restricted to subjects assessed to have received continuous prophylaxis*	PROPHcont

14.2.19.7.4		*Annualized bleeding rates based on Poisson distribution – all types of BEs by severity of BE – during inhibitor-free periods – restricted to subjects assessed to have received continuous prophylaxis*	PROPHcont
14.2.19.6.8 .1	T	*Overall Efficacy Assessment of Prophylactic Treatment (Rate of BEs with 95% confidence interval) - Spontaneous BEs - during time with confirmed inhibitor*	PROPH, PROPHPP
14.2.20	T	*Number of exposure days and infusions administered for on-demand treatment with Human-cl rhFVIII*	On-demand
14.2.21	T	*Statistics on the number of exposure days for on-demand treatment to Human-cl rhFVIII and infusions administered*	On-demand
14.2.22.1	T	*Statistics on the amount of Human-cl rhFVIII (IU) for on-demand treatment per month, per year, per exposure days, per injection and in total*	On-demand
14.2.22.2	T	*Statistics on the dosage of Human-cl rhFVIII (IU/kg)) for on-demand treatment per month, per year, per exposure days, per injection and in total*	On-demand
14.2.23	T	*On-demand: Frequency table on haemostatic agents used under on-demand*	On-demand
		BLEEDING EPISODES	
14.2.24.1	T	*Number and frequency of bleeding episodes (BEs) per subject (overall)*	ITT, PP
14.2.24.2	T	*Number and frequency of bleeding episodes (BEs) per subject - during inhibitor-free periods*	ITT, PP
14.2.25.1	T	*Frequency of bleeding episodes per site of BE and in total (overall)* *- overall* *- during inhibitor-free period*	BLEED, BLEED-PP
14.2.25.2	T	*Frequency of bleeding episodes per site of BE and in total - during inhibitor-free periods*	BLEED, BLEED-PP
14.2.27	T	*Severity of bleeding episodes per type of BE (spontaneous, traumatic, post-operative, other) and in total - during inhibitor-free periods*	BLEED, BLEED-PP
14.2.28.1	T	*Severity of bleeding episodes by site of BE (Frequency counts) - during inhibitor-free periods*	BLEED, BLEED-PP
14.2.28.2	T	*Severity of bleeding episodes by joint/no-joint BEs (Frequency counts) - during inhibitor-free period*	BLEED, BLEED-PP
14.2.29	T	*Treatment duration for bleeding episodes per severity and in total - during inhibitor-free periods (Treatment duration = Time between start of first and end of last administration for the BE)*	BLEED, BLEED-PP
14.2.30.1	T	*Personal efficacy assessment (final outcome) of treatment of bleeding episode - Four point scale*	BLEED, BLEED-PP
14.2.30.2	T	*Personal efficacy assessment (final outcome) of treatment of bleeding episode - Three point scale*	BLEED, BLEED-PP
14.2.30.3 14.2.30.4	T	*Personal efficacy assessment (final outcome) of treatment of bleeding episode during inhibitor-free periods* *- like 14.2.30.1,14.2.30.2, but for inhibitor free periods*	BLEED, BLEED-PP
14.2.31	T	*Statistics on the number of exposure days to Human-cl rhFVIII and dosages administered - during inhibitor-free periods*	BLEED, BLEED-PP
14.2.32.1	T	*Statistics on dose (IU and IU/kg) and number of infusions per bleeding episode per bleeding site and in total*	BLEED, BLEED-PP
14.2.32.2	T	*Statistics on dose (IU and IU/kg) and number of infusions per bleeding episode per bleeding site and in total - during inhibitor-free periods*	BLEED, BLEED-PP
14.2.33	T	*Statistics on dose (IU and IU/kg) per bleeding episode by severity of BE and efficacy - during inhibitor-free periods*	BLEED, BLEED-PP
14.2.34	T	*Statistics on dose (IU and IU/kg) of Human-cl rhFVIII per infusion per bleeding site and in total - during inhibitor-free periods*	BLEED, BLEED-PP
14.2.35	T	*Statistics on dose (IU and IU/kg) of Human-cl rhFVIII per exposure day per bleeding site and in total - during inhibitor-free periods*	BLEED, BLEED-PP
14.2.36	T	*Statistics on dose (IU and IU/kg) of Human-cl rhFVIII per infusion per BE per severity of BE and in total - during inhibitor-free periods*	BLEED, BLEED-PP
14.2.37	T	*Statistics on dose (IU and IU/kg) of Human-cl rhFVIII per month and per year for bleeding episodes - during inhibitor-free periods*	BLEED, BLEED-PP
14.2.38.1	T	*Frequency of bleeding episodes per subject in BLEED population - during inhibitor-free periods (total number and rate per month)*	ITT, PP

14.2.38.2	T	*Frequency of bleeding episodes per subject by type of treatment - during inhibitor-free periods (total number and rate per month)*	ITT, PP
14.2.39	T	*Number of treatment days per bleeding episode - during inhibitor-free periods*	BLEED, BLEED-PP
		SURGERIES	
14.2.42.1	T	*Subjects included in surgery analysis (minor, major, total)*	ITT, PP
14.2.42.2	T	*Number of surgical procedures (minor, major, total)*	SURG, SURG-PP
14.2.43	T	*Surgery Characteristics (basic summary statistics on type, severity and duration)*	SURG, SURG-PP
14.2.44	T	*Efficacy Evaluation of the use of Human-cl rhFVIII in surgical procedures (surgeon at end of surgery, post-operatively [haematologist], overall []jointly by surgeon and haematologist], on four and three point scale)*	SURG, SURG-PP
14.2.46	T	*Statistics on number of infusions and exposure days for surgeries per severity and in total*	SURG, SURG-PP
14.2.47	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 (by severity and total)*	SURG, SURG-PP
14.2.48	T	*Statistics on pre-operative loading dose before surgery (IU and IU/kg) by severity (and total)*	SURG, SURG-PP
14.2.49	T	*Statistics on infusions administered during the surgery (Maintenance doses) - Maintenance doses+: Doses administered between start of surgery and end of surgery*	SURG, SURG-PP
14.2.50	T	*Statistics on infusions administered after end of the surgery*	SURG, SURG-PP
14.2.51	T	*Statistics on expected (average and maximum), actual blood loss and difference between actual and expected blood loss*	SURG, SURG-PP
14.2.52	T	*Statistics on expected and actual duration of the surgical procedure and difference between actual and expected duration*	SURG, SURG-PP
		FVIII:C level and in-vivo recovery data summary figures and tables	
14.2.53.1	T	*Doses administered for recovery assessments – Main study (summary statistics for total dose and dose per kg for recovery assessments)*	ITT, PP
14.2.53.2	T	*Doses administered for recovery assessments – ITI study (summary statistics for total dose and dose per kg for recovery assessments)*	ITT, PP
14.2.54.1-3	F	*FVIII:C profile in final assessment of patients with ITI treatment* *Summarized Plot of FVIII:C profiles (individual curves and mean */- STD plots) - original scale and log-scale (FVIIIC.),* *14.2.54.1 – Local lab* *14.2.54.2 – Central lab: one-stage assay* *14.2.54.3 – Central lab: chromogenic assay* *(only, if sufficient data available)*	ITI
14.2.55.1	T	*Statistics on FVIII concentrations (IU/mL), nominal time points, in patients without inhibitors*	ITT, PP (without inhibitors)
14.2.55.2	T	*Statistics on FVIII concentrations (IU/mL), in patients with inhibitors before inhibitor detection, and at final assessment*	ITT, PP, ITI (with inhibitors)
14.2.56.1	T	*Statistics on in-vivo recovery (IVR) of FVIII:C (% per IU/kg) after injection of Human-cl rhFVIII per scheduled time point in patients without inhibitors*	ITT, PP (without inhibitors)
14.2.56.2	T	*Statistics on in-vivo recovery (IVR) of FVIII:C (% per IU/kg) after injection of Human-cl rhFVIII per scheduled time point in patients with inhibitors before inhibitor detection, during ITI treatment and at final assessment*	ITT, PP, ITI (with inhibitors)
14.2.56.3	T	*Statistics on in-vivo recovery (IVR) of FVIII:C (% per IU/kg) after injection of Human-cl rhFVIII per scheduled time point in patients without inhibitors and continuous prophylaxis*	PROPHcont
14.2.57.1-4	F	*Recovery profiles* *14.2.57.1 - for patients without confirmed inhibitors – Central lab: one stage assay – ITT population* *14.2.57.2 - for patients with inhibitor development - Central lab: one stage assay – ITT population* *14.2.57.3 - for patients without confirmed inhibitors - Central lab: chromogenic assay – ITT population*	ITT

		14.2.57.2 - for patients with inhibitor development - Central lab: chromogenic assay – ITT population	
		RESOURCE USE (additional tables)	
14.2.58	T	*Statistics on the number and duration of hospitalization overall and separated for hospitalizations under prophylaxis, under on-demand and under ITI, as well as separated for with and without inhibitor*	ITT
14.2.59	T	*Statistics on changes in treatment in subjects with inhibitor vs. subject without inhibitor*	ITT
14.2.60	T	*Frequency table on haemostatic agents used in subjects with inhibitor vs. subject without inhibitor*	ITT
14.2.61	T	*Statistics on the use of CVAD*	ITT
		SAFETY	
14.3.1.1.	T	*Extent of exposure (number of EDs and infusions, total dose (IU and IU/kg) per reason for administration and in total)*	SAF
14.3.1.2	T	*Summary of treatment-emergent adverse events (number of subjects/infusions with any AE, SAE, Severe AE or possibly or probably related AE, AEs that begin within 24 hours of end of infusion)*	SAF, Safety-INF
14.3.1.3	T	*Treatment-emergent adverse events by preferred term by subject (descending frequency)*	SAF
14.3.1.4	T	*Treatment-emergent adverse events by preferred term by infusion (descending frequency)*	Safety-INF
14.3.1.5	T	*Treatment-emergent adverse events by system organ class and preferred term*	SAF, Safety-INF
14.3.1.6.1	T	*Treatment-emergent possibly/probably related (acc. to investigator) adverse events by system organ class and preferred term*	SAF, Safety-INF
14.3.1.6.2	T	*Treatment-emergent possibly/probably related (acc. to sponsor) adverse events by system organ class and preferred term*	SAF, Safety-INF
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, Safety-INF
14.3.1.8	T	*Severity of treatment-emergent adverse events by system organ class and preferred term*	SAF
14.3.1.9	T	*Severity of treatment-emergent adverse events by system organ class and preferred term*	Safety-INF
		Sub-group analyses	
14.3.1.12	T	*Summary of treatment-emergent adverse events – by total amount of Human-cl rhFVIII before AEs*	SAF, Safety-INF
14.3.1.13	T	*Treatment-emergent adverse events by system organ class and preferred term – by total amount of Human-cl rhFVIII before AEs*	SAF, Safety-INF
14.3.1.14	T	*Summary of treatment-emergent adverse events – by number of EDs with Human-cl rhFVIII before AEs*	SAF, Safety-INF
14.3.1.15	T	*Treatment-emergent adverse events by system organ class and preferred term – by number of EDs with Human-cl rhFVIII before AE0*	ITI
14.3.1.16	T	*Summary of adverse events – during ITI*	ITI, Safety-INF
14.3.1.17	T	*Treatment-emergent adverse events by system organ class and preferred term – during ITI*	ITI
14.3.1.18	T	*Summary of adverse events – by prophylactic treatment class (on prophylaxis vs. on on-demand)*	SAF, Safety-INF
14.3.1.19	T	*Treatment-emergent adverse events by system organ class and preferred term – by prophylactic treatment class (on prophylaxis vs. on on-demand)*	SAF
14.3.1.20	T	*Summary of adverse events – during and after surgical interventions (up to end of post-surgical treatment)*	SAF, Safety-INF
14.3.1.21	T	*Treatment-emergent adverse events by system organ class and preferred term – during and after surgical interventions (up to end of post-surgical treatment)*	SAF, Safety-INF
14.3.2.1	T	*Treatment-emergent serious adverse events by system organ class and preferred term*	SAF, Safety-INF
14.3.2.2	L	*Listing of Serious Adverse Events list of SAEs : full details including time since last Human-cl rhFVIII treatment, last Human-cl rhFVIII treatment (dose, batch),*	SAF

		hospitalization?, treatment of AE, lab tests performed, relevant medical history, relevant concomitant medication reason for seriousness	
14.3.2.3	L	*Listing of deaths*	SAF
14.3.2.4	L	*List of AEs leading to discontinuation of study medication or deaths*	SAF
14.3.4.1	L	*Abnormal laboratory value listing* *(2 sub-listings: hematology, clinical chemistry)*	SAF
14.3.4.2.1-2	T	*Safety Lab Panel summary statistics for each lab parameter and time point (excluding surgery)* *(2 sub-tables: Hematology, Clinical Chemistry)*	SAF
14.3.4.2.3-4	T	*Safety Lab Panel Change in lab parameter from baseline per time point (excluding surgery)* *(2 sub-tables: Hematology, Clinical Chemistry)*	SAF
14.3.4.2.5-6	T	*Safety Lab Panel summary statistics for each lab parameter before surgery, after surgery and change* *(2 sub-tables: Hematology, Clinical Chemistry*	SAF
14.3.4.3.1	T	*Vital Signs* *Summary statistics on all vital sign determinations per time point (excluding surgery)*	SAF
14.3.4.3.2	T	*Vital Signs: Changes* *Summary statistics on changes in vital sign determinations compared to baseline per time point (excluding surgery)*	SAF
14.3.4.3.3	T	*Vital Signs* *Summary statistics on all vital sign determinations per time point before, during and after surgery*	SAF
14.3.4.3.4	T	*Vital Signs : Changes* *Summary statistics on changes in vital sign determinations during and after surgery compared to before surgery*	SAF
14.3.4.3.5	T	*Physical Examination shift tables on the evaluations of each category included in the physical examination (baseline vs. month 6 visit)*	SAF
16.2		*Listings provided as appendices to the CSR*	
16.2.1.1	L	*Prematurely discontinued subjects (inc. time in study, reason for premature discontinuation, age, total dose, total dose per kg and number of EDs)*	All
16.2.1.2	L	*Study completion* *2 subtables for main and ITI study*	All
16.2.2	L	*Protocol violations flagged by "minor" and "major"*	All
16.2.3	L	*Disposition of subjects with respect to analysis populations*	All screened subjects
16.2.4.1	L	*Subject demographics*	All
16.2.4.2	L	*Medical History*	All
16.2.4.3	L	*Background data*	All
16.2.4.4	L	*F8 gene mutation analysis*	All
16.2.4.5	L	*RNA expression analysis*	All
16.2.4.6.1	L	*Prior and Concomitant Medication*	All
16.2.4.6.2	L	*Relevant concomitant medication in ATC class blood and blood forming organs*	All
16.2.4.6.3	L	*Co medication used in the treatment of bleeding episodes*	BLEED, BLEED-PP
16.2.4.6.4	L	*Concomitant medication with indication surgery*	SURG, SURG-PP
16.2.4.6.5	L	*Relevant concomitant medication in ATC class blood and blood forming organs during hospitalization for surgery*	SURG, SURG-PP
16.2.5.1	L	*Human-cl rhFVIII doses during study including reason for treatment*	All
16.2.5.2	L	*Number of infusions and Human-cl rhFVIII consumption per exposure day*	All
16.2.5.3.1	L	*Subject exposure (duration of participation, EDs, number of infusions) – excluding ITI treatment*	All
16.2.5.3.2	L	*Subject exposure (duration of participation, EDs, number of infusions) – ITI treatment*	All
16.2.5.3.3	L	*Subject exposure (duration of participation, EDs, number of infusions) – Overall (ITI and non-ITI treatment)*	All
16.2.5.4	L	*Subject exposure (duration of participation, EDs, number of infusions) before inhibitor generation*	Patients with inhibitors

16.2.5.5	L	*Doses of Human-cl rhFVIII for recovery determinations*	All
16.2.5.6	L	*Doses of Human-cl rhFVIII for ITI treatment*	ITI
16.2.5.7	L	*Doses of Human-cl rhFVIII for on-demand therapy*	On-demand
16.2.5.8	L	*Human-cl rhFVIII injections for prophylactic treatment during study*	PROPH
16.2.5.9	L	*Exposure days and Human-cl rhFVIII consumption for prophylactic treatment during study*	PROPH
16.2.5.10	L	*Amount of Human-cl rhFVIII for prophylactic treatment per month, per year, exposure day and in total*	PROPH
16.2.5.11	L	*Dose of Human-cl rhFVIII for surgical reasons*	SURG, SURG-PP
16.2.5.12.	L	*FVIII concentrations (IU/mL) per assay during recovery determination*	All
16.2.5.13	L	*Cmax, Cmaxnorm, tmax and recovery of FVIII:C for Human-cl rhFVIII (for both assays, nominal and actual potencies)*	All
16.2.5.14	L	*Half-life and recovery determinations, success criteria for ITI patients*	ITI
16.2.5.15	L	*Pre-, intra-, and post-operative FVIII:C plasma levels (local and central lab)*	SURG, SURG-PP
16.2.6.1	L	*Number of bleeding episodes, rate per month, rate per year, overall efficacy of prophylactic treatment, characteristics of BE (3 subtables for spontaneous, traumatic and all BEs + 3 subtables for prophylactic treatment in inhibitor-free period)*	ITT
16.2.6.3	L	*Bleeding episodes during study (including BEs in BLEED population and BEs not in BLEED population)*	All BEs
16.2.6.4	L	*Bleeding episodes, doses and changes in dose per infusion for each bleeding episode during study*	BLEED, BLEED-PP
16.2.6.5	L	*Bleeding episodes by site of BE, efficacy assessments, doses per BE and per infusion by site of BE*	BLEED, BLEED-PP
16.2.6.6	L	*Other per subject data on BEs in BLEED population*	All
16.2.6.9.1.1	L	*Surgeries: Description and outcome of surgical procedures*	SURG, SURG-PP
16.2.6.9.1.2	L	*Description and outcome of surgical procedures – Criteria for major severity, Hospitalization*	
16.2.6.9.2	L	*Surgeries: Description of wound hematoma yes/no and whether it needed surgical evacuation yes/no*	SURG, SURG-PP
16.2.6.9.3	L	*Surgeries: Description and assignment to SURG/SURG-PP populations including reasons for exclusion*	SURG, SURG-PP
16.2.6.9.4	L	*Surgeries: Blood loss (planned and actual), duration of surgery (planned and actual)*	SURG, SURG-PP
16.2.6.10	L	*Medical resource use data not covered in other listings: CVAD type, CVAD use, complications and management of the complications, hospitalization (including ward type) and duration*	All
16.2.6.11	L	*Additional health economic evaluation*	All
16.2.7.1	L	*Treatment-Emergent adverse Events (inc. indicator for phase of study: prophylactic, surgery, on-demand, ITI)*	All
16.2.7.2	L	*Possibly/probably related treatment-emergent adverse events (according to investigator and/or sponsor)*	All
16.2.7.3	L	*Non-treatment emergent adverse events*	All
16.2.8.1	L	*Laboratory assessments (Haematology, Clinical chemistry) (2 sub-listings: hematology, clinical chemistry)*	All
16.2.8.2	L	*FVIII:C, Inhibitors at baseline and during study*	All
16.2.8.3	L	*Confirmed occurrence of inhibitor, time from ED1 to confirmed inhibitor occurrence and number of EDs before inhibitor development, if any*	All
16.2.8.4	L	*Assessment of success in patients with inhibitors/ ITI therapy*	ITI
16.2.8.5	L	*Epitope mapping (in case of inhibitor development)*	ITI
16.2.8.6	L	*Vital signs*	SAF
16.2.8.7.1	L	*Physical examination*	All
16.2.8.7.2	L	*Abnormal findings of physical examination*	SAF
16.2.9.1	L	*Additional comments provided in the CRF*	All

16.2.9.2	L	*Additional information / observations*	All
16.4		*Individual Subject Data Listings (section 16.4 of the CSR)*	
		Note: SAS datasets including individual subject data will be prepared. Datasets will be available on request, e.g. for an electronic submission according to CDISC /SDTM. Therefore no listings will be prepared for Section 16.4.	

Appendix I: Determination of slope of elimination curve by non-compartmental PK analysis with WinNonlin®

The following is taken from the WinNonlin user's guide [[2] , Chapter 9, pages 218, 219], where K is the rate constant, associated with the terminal elimination phase and the slope of the terminal elimination phase on log scale = - K:

The user may specify the data points to be included in the calculation of K or choose that K not be estimated. If neither of these options is selected, WinNonlin determines the data points to be included, as follows. During the analysis, WinNonlin repeats regressions using the last three points with non-zero concentrations, then the last four, last five, etc. Points prior to C_{max} or prior to the end of infusion are not used unless the user specifically requests that time range. Points with a values of zero for the dependent variable are excluded. For each regression, an adjusted R^2 is computed:

$$Adjusted\ R^2 = 1 - \frac{(1 - R^2) \cdot (n - 1)}{n - 2}$$

Where n is the number of data points in the regression and R^2 is the square of the correlation coefficient.

The regression with the largest adjusted R^2 is selected to estimate K with these caveats:

- If the adjusted R^2 does not improve, but is within 0.0001 of the largest adjusted R^2 value, the regression with the larger number of points is used.
- K must be positive, and calculated from at least three data points.