8HA01EXT

STATISTICAL ANALYSIS PLAN

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Product Studied: Recombinant, Long-acting Coagulation Factor VIII Fc Fusion Protein (rFVIIIFc)

Protocol Number(s): 8HA01EXT

An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor VIII Fusion Protein (rFVIIIFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects With Hemophilia A

Date of Protocol: 26 August 2013 (Version 3)

Date of Statistical Analysis Plan: 10 March 2017

Approved By:

[redacted], Biostatistics — Date

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[redacted], Clinical Research/Drug Safety and Risk Management — Date

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BU	Bethesda Units
BUN	blood urea nitrogen
CHO-KLAT	Canadian Hemophilia Outcomes-Kids' Life Assessment Tool
CRF	Case Report Form
dL	deciliter
DSMC	Data Safety Monitoring Committee
eCRF	Electronic Case Report Form
ED	exposure day
EPD	electronic patient diary
FAS	Full Analysis Set
FVIII	factor VIII
GGT	gamma glutamyl transferase
HCV	Hepatitis C
HIV	human immunodeficiency virus
IU	International Unit
IV	intravenous
IXRS	Interactive Voice/Web Response System
kg	kilogram
MedDRA	Medical Dictionary for Regulatory Activities
MRT	mean residence time
PK	pharmacokinetic
QoL	quality of life
RBC	red blood cell count
rFVIIIFc	recombinant coagulation factor VIII Fc fusion protein
SAE	serious adverse event

SAP	statistical analysis plan
SOC	system organ class
SVC	Single Vial Consolidation
TEAE	treatment-emergent adverse event
vWF	von Willebrand factor
WBC	white blood cell count

1. INTRODUCTION

Hemophilia A is an X-chromosome-linked bleeding disorder caused by mutations and/or deletions in the factor VIII (FVIII) gene resulting in a deficiency of FVIII activity [Mannucci, 2001; Bolton-Maggs and Pasi, 2003]. The coagulation disorder occurs predominantly in males and affects approximately 1 in 10,000 males. The severity of disease is characterized by the endogenous level of FVIII measured in the plasma. Severe hemophilia A is defined as a level of FVIII coagulant activity (FVIII:C) in plasma of <1% (<1 IU/dL). Individuals with severe hemophilia A experience frequent bleeding and recurrent spontaneous bleeding into the soft tissue and joints, leading to joint damage and severe disability. Repeated bleeding into muscles and joints, which often begins in early childhood, results in hemophilic arthropathy and irreversible joint damage. Damage can lead to limited mobility of joints, muscle atrophy, and chronic pain [Rodriguez-Merchan, 2003].

There is no cure for hemophilia A, so treatment focuses on the replacement of FVIII with the intravenous (IV) administration of FVIII-containing coagulation products to promote clotting. The goal of treatment with FVIII-containing coagulation products is to raise the circulating level of FVIII to the lowest effective level to achieve either resolution of bleeding (on-demand [episodic] treatment) or prevention of bleeding (prophylaxis treatment) [WFH, 2005; MASAC, March 2009]. The frequency of administration of FVIII products varies between patients and is tailored to the patient's clinical status, taking into consideration the type of bleeding episode, frequency of bleeding, and the goal of treatment for the subject. The dose of FVIII required also varies and has been based on observations over the years and guidelines established by organizations such as the National Hemophilia Foundation of the United States and the World Federation of Hemophilia (WFH) [WFH, 2005].

This statistical analysis plan is for the purpose of providing an analysis of long term safety and efficacy data on rFVIIIFc to support the generation of long-term data on safety, efficacy and other patient reported outcomes. The analysis is based on study 8HA01EXT data only. Study subjects refer only to those subjects enrolled into this study from parent studies 997HA301, 8HA02PED, 997HA307, and 997HA309. A parent study is defined as a study where subjects may be enrolled into 8HA01EXT after study completion.

2. DESCRIPTION OF OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of the study is to evaluate the long-term safety of rFVIIIFc in subjects with hemophilia A.

2.1.2. Secondary Objective

The secondary objective of the study is to evaluate the efficacy of rFVIIIFc in the prevention and treatment of bleeding episodes in subjects with hemophilia A.

2.2. Study Endpoints

2.2.1. Primary Endpoint

The primary endpoint is the occurrence of inhibitor development.

2.2.2. Secondary Efficacy Endpoints

The secondary endpoints are as follows:

- The annualized number of bleeding episodes (spontaneous and traumatic) per subject
- The annualized number of spontaneous joint bleeding episodes per subject
- The total number of days of exposure per subject per year
- The consumption of rFVIIIFc as total dose per kg per subject per year
- Physician's global assessment of the subject's response to his treatment regimen using a 4-point scale
- Subject's assessment of response to the treatment of bleeding episodes using a 4-point scale

2.2.3. Major Surgery Endpoints

The major surgery endpoints are as follows:

- Investigator/Surgeon assessment of hemostatic response to surgery using the 4-point bleeding response scale
- Number of injections and dose per injection to maintain hemostasis during the surgical period
- Estimated blood loss (mL) during surgery and the post-operative period
- Number of blood product units transfused during surgery

2.2.4. Endpoints Based on Patient-reported Outcomes

Subjects will only take the questionnaires that they completed during the parent study. Subjects who go outside of the age range for a questionnaire should no longer complete the questionnaire. The Investigator will administer the age-appropriate questionnaire at the appropriate visits. The following patient-reported outcomes will be assessed.

Quality of Life (QoL) questionnaires:

- Haem-A-QoL
- Haemo-QoL
- Hemo-Sat-Patient Satisfaction Scale for parents/guardians, Version 15
- Canadian Hemophilia Outcomes-Kids' Life Assessment Tool (CHO-KLAT)
    - Children, Version 2.0 (for children previously enrolled in study 8HA02PED who are less than 18 years of age).
    - Proxy, Version 2.0p (for parents/guardians of children previously enrolled in study 8HA02PED and who are less than 18 years of age)
- EQ-5D Y (referred to as EQ-5D Youth for children in study 8HA02PED)
- EQ-5D-3L (referred to as EQ-5D in study 997HA301)

Health outcomes related to hemophilia will include:

- Number of hospitalizations excluding planned hospitalizations, elective surgery documented at Visit 1, and emergent surgery
- Number of emergency room visits
- Number of physician visits, excluding study visits
- Number of hospitalization days
- Number of days off work, school, day care, or preschool
- Number of days off work for the parent or caregiver

3. STUDY DESIGN

3.1. Overall Study Design and Plan

This is an open-label, multi-center, long-term study of IV administration of rFVIIIFc in previously treated patients (PTPs) with hemophilia A who have completed the A-LONG study (997HA301), the pediatric study (8HA02PED), or any other study with rFVIIIFc that plans to enroll subjects into this study after study completion or at a time specified in the protocol. This is a global study and will be offered to those countries participating in the parent studies.

Based on final and estimated sample sizes from these studies, approximately 214 subjects from studies 997HA301, 8HA02PED, 997HA307, and 997HA309 may be eligible to enroll in this extension study. The End of Treatment (EOT) Visit of the previous study may serve as the initial visit of the extension study. Assessments performed at this visit will be used to confirm eligibility for participation in the extension study.

Study visits are scheduled at 6-month (±2 weeks) intervals following completion of Visit 1. Unscheduled visits may occur as deemed necessary by the Investigator. For subjects who undergo surgery, the Last Post-Operative Visit assessments will be performed when the subjects switch from their post-surgery dosing regimen to a regimen outlined in Section 3.2.1.

For subjects undergoing surgery, post-operative clinic visits may be more frequent. For subjects undergoing major surgery, a visit (Visit 3) is required 1-2 weeks after surgery (not required for minor surgery). A last post-operative visit (Visit 4) is required only if subjects who had major surgery did not return to a regular rFVIIIFc regimen as determined by the Investigator at Visit 3.

All subjects will have the opportunity to continue in this study for up to 4 years or until rFVIIIFc is commercially available in the applicable participating country.

Subjects first dosed with rFVIIIFc when <12 years of age in the parent study will be followed to at least 100 EDs in total across parent and extension study, even if rFVIIIFc becomes commercially available.

3.2. Treatment

Subjects 12 years of age or older will follow either a tailored prophylaxis, weekly prophylaxis, personalized prophylaxis, or episodic regimen based on the clinical profile of the subject and by the trough and/or peak (recovery) values, if needed, as observed in the parent study. Subjects are allowed to change treatment regimens (for example, from tailored prophylaxis to episodic, or from episodic to tailored prophylaxis) at scheduled or unscheduled visits during the study. Subjects less than 12 years of age will receive 1 of 2 prophylactic regimens, tailored or personalized, and will not have the option to change to a weekly prophylactic or episodic regimen, unless they reach the age of 12 years during the study, at which time they can use any of the 4 treatment regimens. All regimen changes must occur at a scheduled or unscheduled clinic visit following assessment by the Investigator, and must be documented at that visit. Details (including date of change, new dose and/or dosing interval, and reasons for the change) will be recorded on electronic case report forms (eCRFs).

3.2.1. Regimens

3.2.1.1. Episodic Regimen

The individual dose of rFVIIIFc to treat bleeding episodes will be based on the subject's clinical condition, type and severity of the bleeding event, and if indicated, FVIII levels. A subject's PK profile and dosing levels from the parent study may also be used to guide dosing decisions. Subjects <12 years of age entering from another rFVIIIFc study will not be offered this option, but can receive an episodic regimen once they reach the age of 12 years during the study.

3.2.1.2. Prophylaxis Regimens

Details for each dosing option, including, if applicable, date of change, new dose and/or dosing interval, and reason(s) for the regimen change will be recorded on the appropriate eCRF each time a change is made.

Option 1: Tailored Prophylaxis

The Investigator may consider the following options for tailored prophylaxis to target a FVIII trough of up to 5%, but is encouraged to use the lowest effective dose targeting a FVIII trough level between 1% and 3%. If bleeding episodes occur at FVIII trough levels of 1% to 3%, further adjustments to dose or interval over the course of the study will target trough levels of up to 5%.

Dosing options are:

- approximately 25 IU/kg to 65 IU/kg every 3 to 5 days
- or dosing 2 times per week at approximately 20 IU/kg to 65 IU/kg on Day 1 and 40 IU/kg to 65 IU/kg on Day 4

The dose and interval should be based on the subject's clinical profile observed in the preceding rFVIIIFc study, and/or his individual PK (if available), and FVIII trough and/or peak (recovery) values.

In pediatric subjects, doses may be adjusted up to a maximum prophylactic dose of 80 IU/kg and the interval decreased to every 2 days, if necessary to maintain adequate FVIII activity trough levels and prevent spontaneous bleeding events.

Option 2: Weekly Prophylaxis

Dosing is approximately 65 IU/kg at weekly intervals. The dose should be based on the subject's clinical profile observed in the parent rFVIIIFc study, and/or his individual PK (if available), and FVIII trough and/or peak (recovery) values. Subjects <12 years of age at entry to 8HA01EXT will not be offered this option initially but may be prescribed this weekly prophylaxis regimen once they reach the age of 12 years during the study.

Option 3: Personalized Prophylaxis

If optimal prophylaxis dosing cannot be achieved using either of the above options, the Investigator may further personalize dosing to meet the needs of individual subjects.

The Investigator may consider the following personalized dosing options:

- Addition of "prevention" doses prior to strenuous activity

- Targeting a FVIII trough level of >3%, if the bleeding history and/or activity level requires
- Dosing less frequently

3.2.2. Surgery and Rehabilitation

If a subject requires emergent or elective surgery while participating in this study, he may be treated with the dose and regimen of rFVIIIFc deemed appropriate for the type of surgery. If a subject had a major surgery before the implementation of Protocol Amendment 2, only major surgeries that were not prescheduled were to be reported as SAEs. However, for subjects having a major surgery after the implementation of Protocol Amendment 2, all major surgeries were to be reported as SAEs.

3.3. Number of Subjects

3.3.1. Sample Size

As this is an extension study, the sample size was based on the planned sample sizes of studies 997HA301 (N=144), 8HA02PED (N=50), 997HA307 (N=12), and 997HA309 (N=8, the subset of subjects from Australia and New Zealand only). This might be increased based upon enrollment being greater than expected in these studies.

3.3.2. Study Sample

Subject inclusion and exclusion criteria can be found in Sections 8.1 and 8.2 of the protocol.

3.3.3. Procedures for Discontinuing Treatment and Removal of Subjects from the Study

A subject *must* permanently discontinue rFVIIIFc for any of the following reasons:

- A Grade 2 or greater allergic drug reaction in association with administration of rFVIIIFc, as defined below by the Recommendations for Grading of Acute and Sub-Acute Toxic Effects on the World Health Organization WHO scale [WHO handbook, 1979]:
  - Grade 2 Bronchospasm related to rFVIIIFc; no parenteral therapy needed
  - Grade 3 Bronchospasm related to rFVIIIFc; parenteral therapy required
  - Grade 4 Anaphylaxis related to rFVIIIFc
- A high-titer inhibitor (≥5.00 BU/mL)
- Use of FVIII products other than rFVIIIFc, unless it occurs in 1 life-threatening emergency and/or as a result of 1 accidental use, and the Sponsor agrees to retain the subject in the study.
- Any condition a subject develops that precludes him from complying with the study procedures.
- The subject experiences a medical emergency that necessitates discontinuation of treatment.

- Clinical judgment of the Investigator: a subject may have treatment permanently discontinued, if in the opinion of the Investigator, it is not in the subject's best interest to continue with the study treatment.
- The parent or legal guardian can withdraw the subject from the study at will at any time.
- The subject and/or his parent/guardian withdraw consent.
- At the discretion of the Investigator or Sponsor for noncompliance

The reason for discontinuation of study treatment must be recorded in the subject's eCRF.

For any subject who no longer responds to treatment with rFVIIIFc, as determined by the Investigator, a decision will be made with the Sponsor whether to continue the subject on the study.

Subjects who discontinue treatment should remain in the study to complete protocol-required tests and assessments, and then must be permanently withdrawn from the study.

3.3.4. End of Study

The end of study is defined as the last subject's last visit. This will occur once all subjects have completed the study, discontinued prematurely, switched to commercially available rFVIIIFc when it becomes available in the applicable participating country, or switched to EAP (Expanded Access Program).

3.3.5. Randomization and Blinding

This is an open-label study with no blinding or randomization.

4. ANALYSIS POPULATIONS

For the purpose of the analysis, analysis populations will consist of subjects who enrolled into study 8HA01EXT from parent studies 997HA301, 8HA02PED, 997HA307, and 997HA309.

4.1. All-enrolled Analysis Set

All subjects who consent to participate in 8HA01EXT will be included in the All-enrolled Analysis Set.

4.2. Full Analysis Set (FAS)

Subjects who receive at least 1 dose of rFVIIIFc in study 8HA01EXT will be included in the Full Analysis Set (FAS). Analyses of efficacy will be performed on the FAS.

4.3. Safety Analysis Set

Subjects who receive at least 1 dose of rFVIIIFc in study 8HA01EXT will be included in the Safety Analysis Set.

4.4. Surgery Subgroup

Surgery subgroup is defined as subjects who have undergone major surgery or have major surgical/rehabilitation periods described in Section 5.3.3 during study 8HA01EXT.

5. DATA HANDLING

This study is being conducted under the sponsorship of Biogen. Data management is being performed under contract with Quintiles in collaboration with Bioverativ. Statistical analysis is being performed by Bioverativ, using SAS® version 9.3 or higher and, where appropriate, additional validated software. This statistical analysis plan (SAP) is based on protocol Version 3, dated 26 August 2013 and will detail analyses to be performed and summaries to be produced for the final Clinical Study Report (CSR).

5.1. General Principles

The following rules will be followed for all applicable analyses contained in this SAP, unless specified otherwise.

Because the subjects from studies 997HA301/997HA307/997HA309 and study 8HA02PED are in different age groups (i.e. ≥12 years of age for studies 997HA301/997HA307/997HA309 and <12 years of age for study 8HA02PED) and may therefore have different safety and efficacy profiles, analyses will be performed separately for the groups of subjects from the parent study or parent studies combined, as described in the table below. Further, the table categories (i.e. age cohort, treatment regimen, etc) by type of analyses for each grouping are also detailed unless specified otherwise.

Groups of subjects from the parent study or parent studies combined	Categories by type of analyses
8HA02PED	Baseline/Concomitant therapy and procedures: Age cohort and overall; treatment regimen (including surgery subgroup) and overall Exposure: Age cohort and overall; treatment regimen and overall Efficacy: Age cohort; treatment regimen Patient-reported outcomes: Age cohort and overall; visit Compliance/surgery/Safety: Visit (if applicable)
997HA301	Baseline/Concomitant therapy and procedures: Treatment regimen (including surgery subgroup) and overall Exposure: Treatment regimen and overall Efficacy: Treatment regimen
997HA301/997HA307/997HA309 combined	

	Patient-reported outcomes: Visit Compliance/surgery subgroup/Safety: Visit (if applicable)
Overall	Compliance/Surgery/Safety: Visit (if applicable)

Where treatment regimen (which is defined as treatment regimen in study 8HA01EXT) is:

- Tailored prophylaxis
- Weekly prophylaxis
- Personalized prophylaxis
- Episodic

Age cohort for subjects from study 8HA02PED is as reported for that study, namely:

- <6 years old
- 6 to <12 years old

Summaries of study 8HA01EXT data will be produced using standard summary statistics. Listings will also only include data from study 8HA01EXT and the treatment regimen associated with each data point, unless specified otherwise. Data collected at unscheduled visits will be included in the definition of the maximum and minimum post-baseline values.

Unless specified otherwise, for the purpose of analyses involving change from baseline during 8HA01EXT, baseline will be defined as the last non-missing measurement (that can be used for data analysis) taken prior to or on the date of 8HA01EXT study Study Day 1 (see Section 5.1.1 for a description of study days). Eligible subjects will be enrolled at End of Treatment (EOT) visit of their parent study (997HA301, 8HA02PED, 997HA307, or 997HA309), which will serve as the Baseline Visit for this extension study (Visit 1). Baseline visit assessments may have been repeated if there was a gap in study treatment (e.g. a gap of greater than 37 days following the EOT Visit for the previous study). Post-baseline values are defined as any assessment taken after 8HA01EXT Study Day 1 (see Section 5.1.1 for a description of study days). In the case of unscheduled visits being taken for the same visit number assigned, the latest available non-missing assessment for that visit will be used for by-visit summaries.

Data collected at the local laboratories will be excluded from the analyses of laboratory data but will be included in the data listing.

5.1.1. Description of Study Days

Definition of Gap

A gap is calculated as:

Date of Visit 1 for study 8HA01EXT – date of the last day of the parent study,

where the last day of the parent study is defined as either 1) the date of the last rFVIIIFc dose for subjects on a prophylactic regimen in study 997HA301, 8HA02PED, 997HA307, or 997HA309, or only had PK injections in study 997HA307 or 997HA309, or 2) the date of the last non-safety follow-up study visit for subjects on the episodic regimen in study 997HA301 or 997HA307 or

subjects who ended the study in a surgical/rehabilitation period in study 997HA301, 8HA02PED, 997HA307, or HA997309.

A listing will be provided for subjects from studies 997HA301, 997HA307 and 997HA309 who had a gap of greater than 7 days and subjects from study 8HA02PED who had a gap of greater than 4 days. These gaps were identified because for the majority of the subjects, the FVIII activity is below 1% after 7 days for subjects from studies 997HA301 997HA307, and 997HA309 and below 1% after 4 days for subjects from study 8HA02PED. In addition, the definition of Study Day 1 will be somewhat different for these subjects with a longer gap, as described below.

For simplicity, the gap of greater than 7 days for subjects from studies 997HA301, 997HA307, and 997HA309 and the gap of greater than 4 days for subjects from study 8HA02PED will be referred to as the gap of greater than 7 or 4 days.

Definition of 8HA01EXT Study Day 1

8HA01EXT Study Day 1 will be used as a reference date to calculate the study day relative to the start of study 8HA01EXT. The definition of 8HA01EXT Study Day 1 depends on the length of the gap.

For 8HA01EXT subjects with no gap or a gap of less than or equal to 7 or 4 days:

In general, 8HA01EXT Study Day 1 is defined as the last day of the parent study, i.e. either 1) the day of the last rFVIIIFc dose for subjects on a prophylactic regimen in study 997HA301, 8HA02PED, 997HA307, or 997HA309, or 2) the day of the last non-safety follow-up study visit for subjects on the episodic regimen in study 997HA301 or 997HA307 or subjects who ended the study in a surgical/rehabilitation period in study 997HA301, 8HA02PED, 997HA307, or 997HA309.

For subjects from studies 997HA307 and 997HA309 who only had PK injections (i.e. no injections in treatment phase) and enroll in 8HA01EXT on a prophylactic regimen, the 8HA01EXT Study Day 1 is either 1) the day of the first study visit if there is a prophylactic dose on that day, or 2) the day of the last non-safety follow-up study visit in studies 997HA307 and 997HA309 if there is no prophylactic dose on the day of the first study visit in 8HA01EXT.

For 8HA01EXT subjects with a gap of greater than 7 or 4 days:

8HA01EXT Study Day 1 is defined as either 1) the date of the first rFVIIIFc dose in study 8HA01EXT for subjects on a prophylactic regimen at the start of study 8HA01EXT, or 2) the day of the first study visit for subjects starting study 8HA01EXT on the episodic regimen or in a surgical/rehabilitation period.

Definition of Study Day

The following definition of Study Day will be used in the analysis:

- 8HA01EXT Study Day: day relative to 8HA01EXT Study Day 1, as defined above.

The start/stop day of events will be calculated as (date of event – date of Study Day 1 + 1) if the date of the event is on or after the Study Day 1 date, or (date of event – date of Study Day 1) if the date of the event is before the Study Day 1 date. Study Day -1 is the day immediately preceding Study Day 1. There is no Study Day 0 in this study.

5.1.2. Data Analysis

Unit body weight dose (IU/kg) for analysis of dosing will be calculated as the total IU (nominal dose) for each injection divided by the subject's most recent weight in kilograms prior to the dose of study drug.

Summaries on change from baseline by study visit will be based on subjects who have both study 8HA01EXT baseline and post-baseline values at the visit being summarized. Each of the post-baseline timepoint summaries will contain a row that provides the mean baseline value for the subjects included in that visit summary. There will also be a row for the baseline median where indicated on the table shells.

5.1.3. Handling of Missing Data

Aside from the following, no imputation of study data will be performed.

- The episodic treatment regimen at the start of study 8HA01EXT will be imputed for the scenario specified in Section 5.3.1.
- The end of PK period of the parent study (997HA307 or 997HA309) and start of study 8HA01EXT will be imputed for the scenario specified in Section 5.3.1.
- The occurrence of a new bleeding episode will be imputed if >72 hours lapse between 2 consecutive injections administered to treat a bleed. Details are provided in Section 7.1.1.

For CHO-KLAT, if a subject has data missing at a particular visit, the total score can still be estimated provided at least 27 of the 35 questions have been answered. If a subject's data cannot be used to calculate an overall score that subject will also be excluded from summaries of individual domains at that visit and will be flagged as excluded from summaries in analysis dataset. Details are provided in Section 7.5.3 and Appendix E.

For HAEMO-QoL and HAEM-A-QoL, Hemo-Sat, EQ-5D-Y and EQ-5D-3L, if a subject has data missing at a particular visit for a domain, the total score and subscores will still be estimated provided the questionnaire makes provision for missing domains in the calculation algorithm of overall score. If a subject's data cannot be used to calculate an overall score that subject will also be excluded from summaries of individual domains at that visit and will be flagged as excluded from summaries in data listings. Details are provided in Sections 7.5.1, 7.5.2, 7.5.4 and 7.5.5 Appendix C, F, G, and D, respectively.

For the analysis of AEs and concomitant medications/procedures, if the stop/start date of an AE/concomitant medication is missing or partial, the corresponding study day will be left blank. However, inferences will be made from the partial and missing dates to classify medications as concomitant, AEs as treatment emergent (or not) and AEs during surgical/rehabilitation period. These inferences are described in Sections 6.4.1 and 8.2, respectively.

5.2. Data Summaries

5.2.1. Continuous Variables

Continuous variables will be summarized using descriptive statistics including the number of non-missing values (n), mean, standard deviation (SD), median, minimum, and maximum.

Where specified in the table shells, the 25th and 75th percentiles will also be provided. Means, medians, and the 25th and 75th percentiles will be presented to one decimal place beyond that with which the data was captured. SDs will be presented to two decimal places beyond that with which the data was captured. Minimum and maximum will be displayed to the same number of decimal places as that with which the data was captured.

Unless impractical within a given table, statistics will be aligned by the decimal place in the summary tables (even though not necessarily displayed in this manner in the table shells).

5.2.2. Categorical Variables

Categorical variables will be summarized by counts and percentages. All percentages will be rounded to one decimal place. The percentage will be suppressed when the count is zero. Unless specified otherwise, the denominator for all percentages will be the number of subjects (or other experimental unit, e.g. bleeding episodes) in each treatment regimen or overall with non-missing data for a given summarization. This number (n) will be included with categorical summaries unless the same variable is also being summarized with descriptive statistics, in which case 'n' will already be provided.

5.3. Study Periods

5.3.1. Treatment Regimens for Analysis

For the purpose of analysis, the treatment regimen in study 8HA01EXT means the actual treatment regimen(s) that subjects follow over the course of the study (i.e., not necessarily the regimen they started on). For example, a subject who starts the study on the tailored prophylaxis regimen and switches to the weekly prophylaxis regimen will appear in both the tailored prophylaxis and weekly prophylaxis regimens in the summaries based on the time he spent in the respective regimens.

Start and End of Treatment Regimens

At the start of study 8HA01EXT, the start date and time of the starting treatment regimen is 8HA01EXT Study Day 1 with starting time defined below:

<u>For 8HA01EXT subjects with no gap or a gap of less than or equal to 7 or 4 days:</u>

In general, starting time is defined as either 1) 1 minute after the last rFVIIIFc dose on 8HA01EXT Study Day 1 for subjects on a prophylactic regimen in study 997HA301, 8HA02PED, 997HA307, or 997HA309, or 2) 23:59 on 8HA01EXT Study Day 1 for subjects on the episodic regimen in study 997HA301/997HA307 or subjects who ended the study in a surgical/rehabilitation period in study 997HA301, 8HA02PED, 997HA307, or 997HA309.

For subjects from study 997HA307/997HA309 who only had PK injections (i.e. no injections in treatment phase) and enroll in 8HA01EXT on a prophylactic regimen, the start time is either 1) the time of the prophylactic dose on Study Day 1, or 2) 23:59 on Study Day 1 if there is no prophylactic dose on Study Day 1. The time between 23:59 and 1 minute before the first prophylactic dose in study 8HA01EXT will be imputed as PK period.

<u>For 8HA01EXT subjects with a gap of greater than 7 or 4 days:</u>

Start time is defined as either 1) time of the first rFVIIIFc dose on 8HA01EXT Study Day 1 for subjects on a prophylactic regimen at the start of study 8HA01EXT, or 2) 00:01 on 8HA01EXT Study Day 1 for subjects starting study 8HA01EXT on the episodic regimen or in a surgical/rehabilitation period.

The above definition of the start date and time of the starting treatment regimen is applicable for all subjects with the following exceptions:

- For subjects who were on the episodic treatment arm in study 997HA301or 997HA307, or only had PK injections in study 997HA307 or 997HA309, and started study 8HA01EXT on the episodic regimen, if there was any dose on 8HA01EXT Study Day 1, then the episodic treatment regimen in study 8HA01EXT will start at the time of that dose.
- For subjects who were on the episodic treatment arm in study 997HA301 or 997HA307 and switched to a prophylactic regimen at study 8HA01EXT start, and had a gap of less than 7 days:
    - If there was no prophylactic dose on the last non-safety follow-up study visit, then the prophylactic treatment regimen in study 8HA01EXT will start at the time of the first prophylactic dose in study 8HA01EXT. The interval from the starting time on 8HA01EXT Study Day 1 (i.e., 23:59 on the day of the last non-safety follow-up study visit) through 1 minute before the first prophylactic dose in study 8HA01EXT will be imputed as the episodic treatment regimen in study 8HA01EXT.
    - If there was a prophylactic dose on the last non-safety follow-up study visit, then the start of the prophylactic regimen in study 8HA01EXT will be the time of that prophylactic dose. In this case, the time from the start of the prophylactic regimen to 23:59 on that day, i.e. the end of the episodic regimen in studies 997HA301 and 997HA307, will be attributed to both study 997HA301/997HA307 and study 8HA01EXT. If there were bleeding episodes during this overlap of time, they would have been attributed to studies 997HA301 and 997HA307.

The end of the last treatment regimen (for subjects who have not changed treatment regimens, it will be the same treatment regimen as they started) will be either 1) the date and time of the last rFVIIIFc dose for subjects whose last treatment regimen was prophylactic or if they were in a surgical/rehabilitation period in study 8HA01EXT, or 2) 23:59 on the day of the last non-safety follow-up study visit for subjects whose last treatment regimen in study 8HA01EXT was episodic.

Treatment Regimen Changes

During study 8HA01EXT, when a treatment regimen changes, the date of the prescribed change will be recorded on the 'Treatment Regimen Assignment Change Details (TRS2)' form in the eCRF. In the following sections, new treatment regimen refers to the one that the subject was changed to, and the previous treatment regimen refers to the one immediately before the new treatment regimen. The start date and time of the new treatment regimen and the end date and time of the previous treatment regimen are defined in the following three scenarios:

- From one prophylactic regimen to a new prophylactic regimen, the new prophylactic regimen starts at the date and time of the first prophylactic dose in the new prophylactic regimen. The previous prophylactic regimen ends 1 minute before that. If the time of the first prophylactic dose in the new prophylactic regimen is not available, the new prophylactic regimen will start at 00:01 on the day of the first prophylactic dose in the new prophylactic regimen, and the previous prophylactic regimen will end at 23:59 on the day prior to that.
- From the episodic regimen to a prophylactic regimen, the prophylactic regimen starts at the date and time of the first prophylactic dose in the prophylactic regimen. The episodic regimen ends 1 minute before that. If the time of the first prophylactic dose in the prophylactic regimen is not available, the prophylactic regimen will start at 00:01 on the day of the first prophylactic dose in the prophylactic regimen, and the episodic regimen will end at 23:59 on the day prior to that.
- From a prophylactic regimen to the episodic regimen, if there is no prophylactic dose on the day of treatment regimen change recorded in the eCRF, the episodic regimen starts at 00:01 on the day of treatment regimen change, and the prophylactic regimen ends at 23:59 on the day prior to the day of treatment regimen change. If there is a prophylactic dose on the day of treatment regimen change, the episodic regimen starts 1 minute after that prophylactic dose, and the prophylactic regimen ends on the date and time of that prophylactic dose.

Duration of a Treatment Regimen

The duration of a given treatment regimen is the time period from the start of the treatment regimen to the end of that treatment regimen in study 8HA01EXT. The duration will stop and start for each treatment regimen change. If a subject is treated in a given treatment regimen more than once in study 8HA01EXT, the total durations in the same treatment regimen will be added together. For example, during study 8HA01EXT, if a subject is treated with the tailored prophylaxis regimen and then the weekly prophylaxis regimen and then goes back to the tailored prophylaxis regimen, then his total duration in the tailored prophylaxis regimen will be the sum of the two durations in the tailored prophylaxis regimen. Further details will be provided for individual analysis where needed.

The total duration of time allocated to each treatment regimen will be calculated in minutes and converted to days as the number of minutes divided by 1440.

5.3.2. Efficacy Period

The efficacy period in study 8HA01EXT will be used for the evaluation of bleeding and consumption endpoints. For a subject to have an evaluable efficacy period over the duration of study 8HA01EXT, he must have >0 day of treatment for an episodic regimen, and at least 2 prophylactic injections for prophylactic regimens.

The start and end, and the total duration of the efficacy period for a given treatment regimen in 8HA01EXT is the same as the start and end, and the total duration of that treatment regimen defined in Section 5.3.1 with the following exception to the definition of start, and the adjustments necessary due to surgical/rehabilitation periods.

Exception to the Definition of Start

For subjects who entered study 8HA01EXT during a surgical/rehabilitation period, if they are to be on a prophylactic regimen in study 8HA01EXT, then the efficacy period for the prophylactic regimen will start at the time of the first prophylactic dose following the end of the surgical/rehabilitation period (see Section 5.3.3). If they are to be on the episodic regimen in study 8HA01EXT, then the efficacy period for the episodic treatment regimen will start at 00:01 on the day following the end of the surgical/rehabilitation period (see Section 5.3.3).

Adjustments Due to Surgical/Rehabilitation Periods

For analysis purposes, the efficacy period for a given treatment regimen will be adjusted for all surgical/rehabilitation periods (major and minor). The start and end of the efficacy period for a given treatment regimen are adjusted as follows:

- For subjects on a prophylactic regimen before the start of a surgical/rehabilitation period, the efficacy period for the prophylactic regimen continues up to the last dose (for prophylaxis or a bleed) before the start of the surgical/rehabilitation period.
- For subjects on the episodic regimen before the start of a surgical/rehabilitation period, the efficacy period for the episodic regimen continues up to 1 minute before the start of a surgical/rehabilitation period.
- For subjects on a prophylactic regimen following the end of a surgical/rehabilitation period, the efficacy period for the prophylactic regimen starts or re-starts (depending on whether there is a treatment regimen change during the surgical/rehabilitation period) at the first prophylactic dose following the end of the surgical/rehabilitation period.
- For subjects on the episodic regimen following the end of a surgical/rehabilitation period, the efficacy period for the episodic regimen starts or re-starts (depending on whether there is a treatment regimen change during the surgical/rehabilitation period) at 00:01 on the day following the end of the surgical/ rehabilitation period.

Start and end dates/times for the efficacy period for given treatment regimens and treatment regimen changes will be adjusted for each surgery (major or minor) as necessary.

For subjects on a prophylactic regimen before the start of a surgical/rehabilitation period, the interval of time between the last dose before a surgical/rehabilitation period and the start of the surgical/rehabilitation period will not be attributed to the efficacy period for the prophylactic regimen. By definition, there should not be any treated bleeding episodes in this interval of time.

For subjects on a prophylactic regimen following the end of a surgical/rehabilitation period, bleeding episodes that occur after discharge from a rehabilitation facility but before the next prophylactic dose will be attributed to the surgical/rehabilitation period and hence not counted towards the annualized bleeding rate.

Adjustments Due to Large Injection Intervals

For analysis purposes, the efficacy period will also be adjusted to account for large intervals between injections resulting from missing data. Time between any 2 adjacent rFVIIIFc injections of greater than 28 days within a prophylactic treatment regimen will be removed from the efficacy period. The efficacy period prior to each such interval will end at the time of the first

injection of this interval and restart (or start if it is the first interval of a treatment regimen) at the time of the second injection of this interval. The efficacy period will be adjusted for each identified interval that is not within a surgical/rehabilitation period. Treatment regimens considered for large interval adjustment include tailored prophylaxis, weekly prophylaxis and personalized prophylaxis regimen with at least 2 routine prophylactic injections (additional injections are not considered due to the sporadic nature of these injections). No adjustment for large injection intervals will be made for episodic treatment regimens.

5.3.3. Surgical/Rehabilitation Period

The broadest span of time for the surgical/rehabilitation period in study 8HA01EXT is from the first dose of rFVIIIFc in study 8HA01EXT given for the surgery (i.e., the pre-surgery dose) up to 1 minute before the first regular prophylactic dose after the last day of postoperative care/rehabilitation for subjects on prophylactic regimens and up to 23:59 on the last day of the surgical/rehabilitation period for subjects on the episodic regimen. If dose(s) labeled for a surgical reasons which do not correspond to a surgery will be re-classified as 'OTHER' and will not be used in the determination of the surgical/rehabilitation period. Since not all subjects will have these events, specific considerations for the start and end of the surgical/rehabilitation period are as follows:

Start of the surgical/rehabilitation period:

- Date/time of the first pre-surgical dose. In general, if an injection for a pre-surgical dose is recorded in the eCRF, the reason for the injection should be labeled as "prophylaxis pre-operative". If an injection for pre-surgical dose is recorded in the EPD, the reason will be labeled as "surgical prophylaxis". If the date/time of surgery is complete, a pre-surgery dose is any dose labeled for a surgical reason on the day of, or the day before surgery, which is prior to the start date/time of the surgery. If the time of surgery is missing or 00:00 (as sometime occurs for minor surgeries), only injections labeled as "prophylaxis pre-operative" on the day of surgery should be taken as a pre-surgical dose along with any other doses labeled for a surgical reason on the day before surgery. If there is more than one pre-surgical dose, then the first one should be selected (a pre-surgical dose can be administered the day before the surgery).
- If there is no pre-surgical dose but there was a prophylaxis dose or dose given for "OTHER" reason prior to the surgery on the day of or the day before surgery, the last of these doses should be selected.
- If there is no pre-surgical dose or a prophylaxis dose prior to the surgery on the day of or the day before surgery then select the start date/time of the surgery. If the time was not recorded or recorded as 00:00 then select the date and impute 00:01 for the time.

End of the surgical/rehabilitation period:

If the treatment regimen after the surgical/rehabilitation period is a prophylactic regimen, then the end of the surgical/rehabilitation period is

- 1 minute before the first prophylactic dose on or after the last date among the dates for discharge from the hospital, post-operative visit 1, post-operative visit 2, the end of rehabilitation.
- If all of the dates mentioned above are missing, then select the first prophylactic dose after the date/time for the end of surgery. If the surgery time was not recorded or recorded as 00:00, then select the surgery date and impute 23:59 for the time. If the end date of the surgery is missing, then select the start date of the surgery and impute 23:59 for the time.
- If there are no prophylaxis doses following the latter of the 6 dates mentioned above, then select the latter of the dates and impute 23:59 for the time if otherwise there is no time associated with the given date (e.g., the subject completed the surgical/rehabilitation period but received no further prophylactic doses).
- If the overall end of study is declared while the subject is still in the surgical/rehabilitation period, then select the date of the end of study and impute 23:59 for the time.

If the treatment regimen after the surgical/rehabilitation period is the episodic regimen, then the end of the surgical/rehabilitation period is

- Imputed as 23:59 on the last date among the dates for discharge from the hospital, post-operative visit 1, post-operative visit 2, and the end of rehabilitation
- If all of the dates mentioned above are missing, then the select the date of the end of surgery and impute 23:59 for the time. If the end date of the surgery is missing, then select the start date of the surgery and impute 23:59 for the time.

Two exceptions are noted:

- If 2 (or more) major surgeries are performed without an intervening discharge from the hospital, then the first surgical/rehabilitation period will end 1 minute before the start of the next surgery and the second surgical/rehabilitation period will end as described above.
- If minor surgery is performed during postoperative care or rehabilitation then the surgical/rehabilitation period for the minor surgery will start and end on the day of the minor surgery, at 00:01 and 23:59, respectively, if times are not otherwise provided or recorded as 00:00. The surgical/rehabilitation period for the major surgery will include the minor surgery (ie, the surgical/rehabilitation period for the major surgery does not stop and restart around the minor surgery) and will end as otherwise defined.

Within the total surgical/rehabilitation period, the time is divided into:

- Intraoperative period: from the date/time of the pre-surgery rFVIIIFc dose to the date/time of the end of surgery
- Postoperative care period: from the date and time plus 1 minute following the end of surgery to the last dose of rFVIIIFc given for the surgery, including doses given to prevent bleeding during the postoperative period

- Postoperative rehabilitation period: from the date following the last day of postoperative care to the end of the surgical period as described above

The surgical/rehabilitation period will be determined in the same manner for both major and minor surgeries.

5.3.4. Safety Period

The safety period is defined as the period from 8HA01EXT Study Day 1 to the last recorded date. The end of the safety period will be imputed as 23:59 for the time on the last recorded date in the analysis database. The last recorded date is either the date of the last study visit, last telephone call, or the date of the last dose, whichever comes last.

5.4. Electronic Patient Diary (EPD) Data

From approximately 25 Apr of 2016, EPD data cannot be queried for changes which require subject confirmation. However a subset of data issues needing changes which do not require subject confirmation may be handled programmatically. One such issue falls under the heading of Single Vial Consolidation (SVC) and occurs when a dose consists of an injection which uses more than one vial and these vials are erroneously recorded in the EPD as separate injections, albeit within a short time window. As a scenario where these are actually 2 separate doses within a short space of time is medically implausible, these vials can be consolidated into a single record for the dose. The programming algorithm can be summarized as follows

- Identify all injection records within 60 minutes of one another (fields for identification are subject ID and injection date/time)
- Exclude all examples of true duplicates, based upon records with a selected number of key fields identical (fields for identification are subject ID, injection date/time, nominal dose, and lot numbers)
- For the remaining pairs of records:
  Exclude them if the reasons for injections are different from each other with the following three types of scenarios: 1) bleed and prophylaxis/additional/OTHER, 2) surgery and prophylaxis/additional/OTHER, and 3) one with the reason that is not provided. Otherwise,
  - Record with earliest injection date/time retained with corresponding contextual information
  - Combine/sum field values related to the dose (e.g. lot numbers, number of vials, volume injected, nominal and actual dose) into the single retained record

6. STUDY SUBJECTS

6.1. Disposition of Subjects

Subject disposition will be summarized for study 8HA01EXT for subjects from each parent study and overall. This table will present the number of subjects in the All-enrolled Analysis Set, the number and percentage of subjects enrolled in the Full Analysis Set (FAS) including the number of subjects with an efficacy period, the number of subjects within each treatment regimen, the number and percentage of subjects in the Safety Analysis Set, and the number and percentage of subjects in the surgery subgroup. The number of subjects with the status of completed, and discontinued from the study, including the primary reason for those who discontinued, will be tabulated. Subject disposition, including the date of the last visit and the reason for early termination for subjects who did not complete the study, will be provided in a data listing.

The number and percentage of enrolled subjects will be summarized by country, site and treatment regimen using All-enrolled Analysis Set. The number of subjects attending each visit in study 8HA01EXT will be summarized overall by planned visit using the Safety Analysis Set. The summary for each study visit will include only those subjects for whom the visit evaluations reflect the designated visit on the study (i.e., including subjects for whom this visit represents the end-of-study visit due to early termination).

6.2. Demography and Baseline Disease Characteristics

Demographics and baseline disease characteristics will be summarized using the Safety Analysis Set.

6.2.1. Demography

Demographic characteristics including age (years), geographic location, height (cm), weight (kg), and body mass index (kg/m^2) will be summarized using the data at entry into study 8HA01EXT. Race and ethnicity will also be included in the summary using the data at the entry into the parent study. Geographic locations are defined as Europe, North America, and other. For subjects from studies 997HA301/997HA307, Europe includes Austria, Belgium, Germany, France, United Kingdom, Italy, Spain, Sweden and Switzerland. North America includes Canada and the United States. Other countries include Australia, Brazil, Hong Kong, India, Japan, Israel, New Zealand and South Africa. For subjects from study 8HA02PED, Europe includes Ireland, the Netherlands, Poland, and the United Kingdom. North America includes the United States. Other countries include Australia, Hong Kong, and South Africa. For subjects from study 997HA309, there are only two countries: Australia and New Zealand, which will be categorized as 'Other'.

6.2.2. General Medical and Surgical History

An updated medical and surgical history is collected at the first visit of study 8HA01EXT. A summary of this updated medical and surgical history by body system for the Safety Analysis Set

will be presented. A subject will be counted only once if they reported one or more occurrences in the same body system.

6.2.3. Physical Examination

Physical examination continues to be performed annually in this extension study. A listing of subjects with an abnormal status will be presented.

6.3. Protocol Deviations

All protocol deviations will be recorded throughout study 8HA01EXT. Major and minor protocol deviations/violations are to be pre-specified prior to database lock. All major protocol deviations during study 8HA01EXT will be summarized by study 8HA01EXT treatment regimen, the surgery subgroup, and overall using the FAS. Protocol deviations that occurred during surgical/rehabilitation periods will be attributed to the surgery subgroup only. All deviations, both major and minor, will be provided in a data listing.

In addition, another set of protocol deviations (PDs) will be determined using the EPD dataset created for the impact analysis, where changes requiring subject confirmation have been reverted to the original pre-change state. Details specific to the impact analysis will be provided in Sections 9 below. This set of PDs will be summarized and listed in a similar manner to the primary set, for the FAS.

6.4. Non-study Drug Medications

6.4.1. Concomitant Medications

Two listings will be provided, one for concomitant medications taken through the Final Study Visit/Early Termination Visit and the other for concomitant medications taken after the Final Study Visit/Early Termination Visit and prior to the Follow-up visit/phone call.

Concomitant medications will be summarized using for the Safety Analysis Set.

Concomitant medications are those administered on or after 8HA01EXT Study Day 1, or administered prior to 8HA01EXT Study Day 1 and ongoing at the start of 8HA01EXT Study Day 1. They will be characterized based on the start and end dates relative to 8HA01EXT Study Day 1. Medications reported for a subject will be classified as concomitant unless they can be excluded as such, as follows:

- Medications with a start date after the follow-up visit will not be considered concomitant.
- For partial dates, if a concomitant medication start day is missing then the medication will be assumed to be a concomitant medication unless the start month and/or year or medication stop date can be used to determine if a medication is concomitant, as follows.
  - If the concomitant medication start day is missing, but the month and year are before the start month and year of 8HA01EXT Study Day 1 and the concomitant medication stop date is before the date of 8HA01EXT Study Day 1, then the medication will not be classified as concomitant.

- If the day of the start date is missing and the month and year are after the month and year of 8HA01EXT Study Day 1, then the medication will be classed as concomitant.
- If the month of the start date is missing and the year is before the start year of 8HA01EXT Study Day 1 and the stop date is before the date of 8HA01EXT Study Day 1, then the medication will not be classified as concomitant.

Concomitant medications will be coded using World Health Organization drug enhanced dictionary version March 2011.

6.4.2. Other Therapies and Procedures

Other therapies administered and concomitant procedures performed in study 8HA01EXT will be summarized using for the Safety Analysis Set as well as will be listed.

6.5. Study Drug

Study treatment regimens are described in Section 3.2. The listing of all study drug administered will include the reason for administration (prophylaxis [regular or additional], treatment of a bleeding episode, surgery, other). Subject-level information on dosing with study drug will also be provided in a data listing.

Treatment with study drug, (exposure, prophylactic dose, prophylactic dosing interval, and consumption) will be summarized using the FAS.

6.5.1. Exposure

6.5.1.1. Duration of rFVIIIFc Dosing, Number of Injections and Exposure Days to rFVIIIFc

Two summaries of exposure will be produced. Details of the summaries are described in Section 7.3.2.

6.5.1.2. Last Prescribed Dose and Dosing Frequency

Subjects' last prescribed dose and dosing frequency will be summarized as a cross tabulation of dosing frequency by dose (IU/kg) in which the number and percentage of subjects who were last prescribed each combination of dose and dosing frequency (every 2, 3, 4, or 5 days or twice weekly) will be tabulated. A summary table will be provided for the overall prophylaxis regimen consisting of the tailored prophylaxis and weekly prophylaxis regimens in study 8HA01EXT. The last prescribed dose will also be summarized for each dosing frequency using descriptive statistics. If no dose (dosing frequency) changes were prescribed, then a subject's starting dose (dosing frequency) will be used. The dose for the twice weekly regimen will be the average of the two doses given. Percentages will be based on the number of subjects in each prophylactic regimen (ie, not on the number of subjects in each dosing frequency category).

6.5.2. Change of Treatment Regimens

For the changes in treatment regimens in study 8HA01EXT described in Section 5.3.1, the number of subjects with at least one treatment regimen change, the regimen first changed to, and the number of changes will be summarized by starting treatment regimen in study 8HA01EXT and overall.

6.5.3. Prophylactic Dose (IU/kg) and Dosing Interval (days)

Because prophylactic dosing in study 8HA01EXT is based on variable doses and dosing intervals, the amount of rFVIIIFc received prophylactically will be summarized as an average weekly dose. Descriptive statistics will be provided using the FAS for each prophylactic regimen.

The average weekly prophylactic dose (IU/kg) and the prophylactic dosing interval will be based on prophylactic doses that are not separated by a bleeding episode. Data to be included in the calculations, specifically the prophylactic doses and the total duration of prophylaxis treatment, will come strictly from intervals representing 2 consecutive prophylactic doses (PR) during the efficacy period (see Section 5.3.2 for a description of the efficacy period). The sum of doses at PR_x and the sum of interval durations (PR_{x+1} minus PR_x) will be determined across all evaluable intervals of PR_x to PR_{x+1}. As such, when a bleeding episode is encountered, the interval stops at the prophylactic dose prior to the event and continues with the first prophylactic dose after the event. The last PR dose during a given treatment regimen will be the end of the last interval used for these calculations. The start and stop time of a treatment regimen and the calculation of total duration in that treatment regimen are described in Section 5.3.1. If a subject is treated in a given treatment regimen more than once during study 8HA01EXT, the sum of doses at PR_x, sum of days in PR intervals, sum of days in PR intervals and number of PR intervals will be calculated across all durations in that treatment regimen before the average weekly prophylactic dose and dosing interval are calculated using the formulae below.

$$\text{Average weekly prophylactic dose} = \frac{\text{Sum of doses at } PR_x}{\text{Sum of days in PR intervals}} \times 7$$

$$\text{Average prophylactic dosing interval} = \frac{\text{Sum of days in PR intervals}}{\text{Number of PR intervals}}$$

For the personalized prophylaxis regimen, additional injections administered will also be included in the average weekly prophylactic dose and average dosing interval calculations.

Prophylactic dosing will be further characterized by the number of prescribed changes in the dose and the number of prescribed changes in the dosing interval while on a given prophylaxis treatment regimen. If both dose and dosing interval change, they will be included in each summary. Dose and dosing interval changes are based on recommendations made by the Investigator and may or may not reflect whatever modifications a subject actually made to his dosing regimen. The number of prescribed changes in the dose level and the number of prescribed changes in the dosing schedule will be summarized categorically (0, 1, 2, 3, 4, >4) and with descriptive statistics. If a subject is treated in a given treatment regimen more than once during study 8HA01EXT, then the total number of changes will be across all durations in that treatment regimen.

6.5.4. Consumption

The total annualized rFVIIIFc consumption (IU/kg) will be calculated for each subject using the following formula:

$$\text{Annualized consumption} = \frac{\text{Total IU/kg of study drug received during the efficacy period}}{\text{Total number of days during the efficacy period}} \times 365.25$$

The total amount of rFVIIIFc received will be the sum of the nominal IU/kg administered for each injection based on the units of rFVIIIFc as recorded from the subject's diary and eCRF and his most recent weight.

Total annualized rFVIIIFc consumption will be determined for each treatment regimen during the efficacy period (i.e., excluding surgery/rehabilitation periods [major and minor surgeries]).

For personalized prophylaxis regimen, additional injections administered will be included in the consumption calculations.

Consumption is a secondary endpoint in this study. A description of how consumption will be summarized is provided in Section 7.3.3.

6.5.5. Compliance

Prophylactic dose compliance will assess adherence to the Investigator's recommendations for dosing. Prophylactic dose compliance will be assessed during the efficacy period.

The prophylactic dose compliance rate will be summarized for overall prophylaxis regimen for the FAS. See Section 6.5.5.2 for further details on prophylactic dose compliance.

Except for doses administered in the clinic, study treatment may be administered by a caregiver or self-administered by the older children in the study.

Data from the eCRF and EPD will be considered for the analysis of treatment received and subjects' compliance with the study protocol; compliance has been defined by the Sponsor. Compliance with prestudy FVIII will not be a considered measurement for this study.

6.5.5.1. Compliance in the Treatment of Bleeding Episodes

Bleeding episodes are defined in Section 7.1.1. All bleeding episodes during the efficacy period for which there is a date and time for both the onset of the bleed and treatment of the bleed will be evaluated for compliance. Compliance will first be determined on a per-bleed basis and then on a per-subject basis. That is, compliance for each bleeding episode will be determined and then the overall percentage of bleeding episodes for which treatment was in compliance will be determined for each subject.

The definition of compliance for the treatment of an individual bleeding episode, as specified by the Sponsor, is no more than 8 hours between the onset of the bleed and the initiation of treatment for the bleed. Thus, the compliance rate for the treatment of bleeding episodes will be measured by determining the proportion of injections administered within a maximum of 8 hours of the initial sign of a bleed, as follows:

$$\text{Treatment of bleed compliance rate} = \frac{\text{Number of first injections to treat a bleed taken within 8 hours of the first sign of a bleed}}{\text{Total number of evaluable bleeding episodes}} \times 100$$

The following circumstances result in a bleeding episode being considered not evaluable for the determination of this compliance rate:

- the type of bleed has been classified as Unknown based on the definition of a bleeding episode (>72 hours between consecutive injections) since there is no onset time
- a missing bleed time for a spontaneous or traumatic bleed
- a bleed time that was recorded as being after the time of treatment

Bleeding episodes for which the first injection for treatment was with non-study drug will be included in the evaluation of compliance. Inclusion of bleeding episodes treated with non-study drug is discussed in Section 7.1.1.

Descriptive statistics of the per-subject compliance rate as well as a categorical summary of these data (<80%, ≥80%) will be presented for overall treatment regimen for the FAS.

6.5.5.2. Compliance of Prophylactic Injections

The compliance rate of each subject to the prescribed prophylactic dosing regimen during the efficacy period will be calculated in 2 ways, as dose compliance and as dosing interval compliance. Compliance will first be determined on a per-injection basis and then on a per-subject basis. That is, compliance for an individual dose or dosing interval will be determined and then the overall percentage of doses and dosing intervals that were in compliance will be determined for each subject.

For the purpose of evaluating compliance, the following will be considered per injection:

- the nominal dose taken compared to the nominal dose prescribed
- the actual day of treatment compared to the prescribed day of treatment

An individual dose will be considered compliant if it is within 80% to 125% of the prescribed dose. An individual dosing interval will be considered compliant if the time between two prophylactic doses is within 24 hours of the prescribed dosing interval. Prescribed dose and dosing intervals are according to the Investigator. Instructions provided to the subject by the Investigator regarding dose or dosing interval changes will be used to determine compliance as of the date the information was provided to the subject.

The actual dosing intervals will be calculated as the length of time between consecutive prophylactic doses (date/time of PR_{x+1} – date/time of PR_x). PR_{x+1} and PR_x are also discussed in Section 6.5.3. The actual time between doses will be determined in minutes and converted to days as the number of minutes divided by 1440. The prescribed dosing interval will be taken from the eCRF as recorded by the Investigator. The absolute value of the difference between the actual and prescribed dosing intervals must be ≤1 day (+/- 24 hours) in order to be compliant.

All prophylactic injections will be used to determine prophylactic dose compliance; only the prophylactic injections used to determine the average prophylactic dosing interval (i.e., intervals

not separated by a bleeding episode or surgical/rehabilitation period), as detailed in Section 6.5.3, will be used to evaluate prophylactic interval compliance. Dose and dosing interval compliance rates per subject will be determined as follows:

$$\text{Dose compliance rate} = \frac{\text{Number of doses taken within 80\% to 125\% of prescribed dose}}{\text{Total number of doses}} \times 100$$

where the percentage of a prescribed dose is calculated as: (nominal dose taken/prescribed dose) x100

and the 'nominal dose taken' will be determined from the nominal potency labeled on the vials used by the subject for each injection of rFVIIIFc.

$$\text{Dose interval compliance rate} = \frac{\text{Number of doses taken within +/- 24 hours of prescribed day/time}}{\text{Total number of intervals}} \times 100$$

A subject is considered 'dose compliant' or 'dosing interval compliant' if his respective rate is at least 80%.

Descriptive statistics of the percentage of nominal doses taken per subject within the 80% to 125% range for dosing compliance as well as frequencies for the dose compliance rate (<80%, ≥80%) will be presented for overall prophylaxis regimen for the FAS. Similarly, descriptive statistics of the percentage of doses taken per subject within ±24 hours of the prescribed day as well as frequencies of the dosing interval compliance rate (<80%, ≥80%) will be presented for the FAS.

Based on their per-subject compliance rates for dose and dosing interval (each <80%, ≥80%), subjects will be further classified into the following mutually exclusive categories for overall compliance to their prophylactic treatment as:

- Both dose and interval compliant
- Dose compliant or interval compliant (but not both)
- Neither dose nor interval compliant

6.5.5.3. Compliance of EPD Contemporaneous data entry

Injections must be entered into the EPD within 7 days from the date of the injection. Injections entered outside the 7-day window will be reported as protocol deviations. Descriptive statistics of the percentage of the subjects with fewer than 80% of their total individual EPD records entered within this 7-day window and those with 80% or greater of records that met this criteria will be presented for overall treatment regimen for the FAS.

The analysis of ABR, duration of dosing, and adverse events in safety, as described in Sections 7.3.1, 7.3.2, and 8.2.1 respectively, will be presented by subgroups based upon this percentage.

7. EFFICACY AND PHARMACOKINETIC ANALYSIS

7.1. General Efficacy Principles

Unless specified otherwise, only data occurring during the efficacy period will be used in analyses and summaries relating to bleeding, consumption, and compliance in the treatment of bleeding episodes; efficacy data collected during the surgical/rehabilitation periods (major and minor) will not be included (see Section 5.3.1).

7.1.1. Bleeding Episodes

Bleeding episodes will be recorded in both the EPD and eCRF; this information will be used to derive the secondary efficacy endpoints. During the course of the study the investigator was given the opportunity to disagree with the type of bleed (spontaneous, traumatic) as classified by the subject/caregiver and the subject/caregiver was subsequently given the opportunity to agree or disagree with the reclassification. If the subject/caregiver agreed with the Investigator's assessment, then all analyses subset by type of bleed will be based on the Investigator's determination of the bleed type whether or not the change was made to the subject's records.

A standardized definition of a bleeding episode has been applied to this study, as follows. A bleeding episode starts from the first sign of a bleed, and ends no more than 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, are considered the same bleed. Any injection to treat the bleed taken more than 72 hours after the preceding one will be considered the first injection to treat a new bleed. For the purpose of analysis, the latter injection will be associated with a new bleeding episode and classified as type=Unknown. The location(s) associated with the original bleeding episode will be carried forth to the new bleeding episode; the onset date and time of bleeding will be unknown and hence considered missing. Any bleeding at a different location is considered a separate bleeding episode regardless of the time from the last injection.

This algorithm will also apply when a follow-up injection was recorded subsequent to a prophylactic injection. If the follow-up injection was administered >72 hours after the previous injection to treat a bleeding episode (type=spontaneous, traumatic, follow-up), then the follow-up injection will be classified as a new bleeding episode as described above.

Bleeding at a different location will occur when the general bleeding location is different (e.g., in a joint for the original bleeding episode and subsequently in a muscle) or in a sub-location not initially present if in the same location category (e.g., right elbow for the original bleeding episode and subsequently in the right and left elbows). Conversely, a bleeding episode that originally occurs in the right elbow and left knee and is reported as a new bleed within 72 hours as being only in the right elbow will be considered to be in the same location and hence not counted as a new bleeding episode.

A bleeding episode that occurs in multiple locations will be counted as a single event when determining the overall annualized number of bleeding episodes. However, in summaries by bleeding location, the bleeding episode will be counted in each location for which it is reported with the exception that bleeding that occurs in more than one sub-location of the same location category (e.g., 2 or more different joints) will be counted as just one for that location category.

Only bleeding episodes that were treated with at least one dose of FVIII (whether rFVIIIFc or a non-study drug) will be included in the analysis of endpoints evaluating bleeding. That is, bleeding episodes that were not treated at all will not be included. Bleeding episodes that were treated with non-study medication will be included in the determination of the annualized bleeding rate. The handling of bleeding episodes treated with non-study FVIII for other endpoints is discussed in Sections 7.4.1.

Bleeding episodes of an unknown type will be included in the determination of the annualized bleeding rate and in summaries based on bleeding episodes but, unless specified otherwise, will not be included in summary tables where endpoints are summarized by type of bleed.

The per-subject annualized number of bleeding episodes, hereafter referred to as the annualized bleeding rate (ABR), will be calculated for each subject using the following formula:

$$\text{ABR} = \frac{\text{Number of bleeding episodes during the efficacy period}}{\text{Total number of days during the efficacy period}} \times 365.25$$

7.1.2. Multiplicity

Multiplicity is not a concern in this study since no statistical tests are being performed on the efficacy endpoints.

7.2. Primary Endpoint

There are no primary efficacy endpoints in this study.

7.3. Secondary Endpoints

7.3.1. Annualized Bleeding Rate

The ABR will be summarized using categorical (e.g. 0, >0-5, >5-10, >10-20, etc.) and descriptive statistics for the FAS. All types of bleeding episodes (spontaneous, traumatic, and type unknown) will be included in determining the annualized number.

As a description of the raw data collected in this study, the unadjusted number of bleeding episodes per subject will be summarized using categorical (e.g. 0, 1-3, 4-6, 7-10, 11-15, etc.) and descriptive statistics over all bleeding episodes and by type of bleed (spontaneous, traumatic, and type unknown). The number and percentage of subjects experiencing a bleeding episode will be summarized categorically for any bleeding episode and for each type of bleed by location (joint, muscle, internal, skin/mucosa, unknown); percentages will be based on each treatment regimen in study 8HA01EXT for FAS. Of note, the number of subjects with a bleeding episode for which the location is unknown will be tabulated in these summaries but no further analysis of unknown bleeding locations is planned. The total subject years followed will be provided in order to put the unadjusted numbers in perspective.

In addition, summaries of the ABR will also be provided for the following subgroups:

- type of bleed (spontaneous, traumatic)
- location of the bleed (joint, muscle, internal, skin/mucosa)
  For the purpose of analysis bleeding episodes with a location of iliopsoas will be

treated as a muscle bleed; however, the location will be displayed as iliopsoas in the listings.

- other combinations of type and location of bleed (spontaneous muscle, spontaneous internal, spontaneous skin/mucosa, traumatic joint, traumatic muscle, traumatic internal, traumatic skin/mucosa)
- target joint at screening in the parent study
- contemporaneous entry compliance of </≥ 80%, as described in Section 6.5.5.3.

7.3.2. Total Number of Days of Exposure

The total number of exposure days (EDs) along with the duration of dosing to rFVIIIFc and total number of injections per subject will be summarized. The summary will use the Safety Analysis Set; these data will be summarized.

In this summary, for any subject, the total number of EDs, duration of dosing to rFVIIIFc, and total number of injections will be calculated from the start date and time of the the starting treatment regimen to the end date and time of the last treatment regimen in study 8HA01EXT. The start and end of treatment regimens are defined in Section 5.3.1. An ED is a 24-hour period in which one or more rFVIIIFc injections are given. The 24-hour window starts from the first rFVIIIFc injection on the study and then for subsequent injections, it starts from an injection taken after/outside of a previously identified ED.

The total number of EDs on rFVIIIFc for each subject will be summarized categorically (<50, 50-<100, 100-<150, 150-<200, 200-<250, etc.) and with descriptive statistics. The total number of injections per subject will be summarized using descriptive statistics.

Any interruptions to dosing will be ignored for the purposes of calculating the interval. The number and percentage of subjects whose duration of dosing was at least 13 weeks, at least 26 weeks, at least 39 weeks, at least 52 weeks, and at least 78 weeks will be tabulated based on the integer part of the calculated week.

Duration of rFVIIIFc dosing (weeks) will also be summarized using descriptive statistics. Weeks will be represented in the descriptive statistics as if these were data collected with 1 decimal place.

This table will also be presented by subgroup based upon contemporaneous entry compliance of </≥ 80%, as described in Section 6.5.5.3.

7.3.3. Total Annualized rFVIIIFc Consumption

The secondary endpoint of total annualized rFVIIIFc consumption per subject for the prevention and treatment of bleeding episodes will be summarized for the FAS. See Section 6.5.4 for details on the annualized rFVIIIFc consumption derivation.

7.3.4. Physician's Global Assessment of the Subject's Response to His rFVIIIFc Regimen

Investigators will record assessments of each subject's response to his rFVIIIFc regimen at each scheduled visit using the following 4-point scale:

1=Excellent: bleeding episodes responded to ≤ the usual number of injections or ≤ the usual dose of rFVIIIFc, or the rate of breakthrough bleeding during prophylaxis was ≤ that usually observed.

2=Effective**:** most bleeding episodes responded to the same number of injections and dose, but some required more injections or higher doses, or there was a minor increase in the rate of breakthrough.

3=Partially Effective: bleeding episodes most often required more injections and/or higher doses than expected, or adequate breakthrough bleeding prevention during prophylaxis required more frequent injections and/or higher doses.

4=Ineffective: routine failure to control hemostasis or hemostatic control requires additional agents.

Investigators should consider the following, if available, when making the assessment:

- Frequency of rFVIIIFc injections
- Response to rFVIIIFc injection
- Information reported in the eDiary by the subject

The physician's global assessment of the subject's response will be summarized by visit for overall treatment regimen for the FAS. The number and percentage of subjects in each response category will be tabulated. Percentages will be based on the number of subjects for whom an assessment was provided at the respective visit. This table will also include a cumulative tabulation across all scheduled study visits; subjects can be included in this tabulation up to all visits, once for each visit. Percentages for this collection of responses throughout the study will be based on the total number of assessments across all visits. In addition, these assessments will be provided in a data listing.

7.3.5. Subject's Assessment of Response to rFVIIIFc Injections for Bleeding

Each subject or subject's caregiver will provide an assessment of response to each administration of rFVIIIFc for each bleeding episode using the 4-point scale of excellent, good, moderate, and none (see Appendix A for further details; 'none' means that there was no improvement, not that the subject did not provide a response). Response categories of excellent and good will be presented combined as well as individually. The number and percentage of injections in each response category will be tabulated based on all injections. Two summaries will be provided. In the first summary percentages will be based on the total number of injections administered for bleeding episodes for which a response was provided. In the second summary percentages will be based on the total number of bleeding episodes whether or not a response was provided. As a supplemental analysis, similar summaries will be provided based on just the first injection administered after each bleeding episode using both approaches to determine the percentages.

- The subject's assessment of response will be summarized for the FAS.

7.4. Additional Assessments

7.4.1. Number of Injections and Dose of rFVIIIFc to Resolve a Bleeding Episode

The number of injections, average dose per injection (IU/kg), and total dose (IU/kg) required to resolve a bleeding episode will be determined on both a per-bleeding episode and per-subject basis. See Section 7.1.1 for details on the definition of a bleeding episode. A bleeding episode is considered resolved when treatment for the bleeding is no longer needed.

Per bleeding episode: The total number of injections will include the initial injection for a spontaneous bleed (SB), a traumatic bleed (TB), or a bleed of unknown type plus all injections identified as follow-up (FU) treatment for that bleed. For each bleed, the average dose per injection will be calculated as the average of all doses (IU/kg) administered among the SB/TB/Unknown and FU injections administered to treat that bleed; the total dose will be the sum of these doses. The number of injections required for the resolution of a bleeding episode will be summarized across all bleeding episodes in study 8HA01EXT both categorically (1, 2, 3, >3; 1, >1; and ≤2, >2) and with descriptive statistics. The average dose per injection and total dose required for resolution of a bleeding episode will be summarized using descriptive statistics.

Per subject: The number of injections, average dose per injection, and total dose required to resolve each bleeding episode, as determined for the per-bleeding episode summaries, will be averaged across all bleeding episodes in study 8HA01EXT for each subject. The average number of injections required for resolution of a bleeding episode will be summarized both categorically (1 to <2, 2 to <3, and ≥3) and with descriptive statistics. The averages for the per-subject average dose per injection and total dose required for resolution of a bleeding episode will be summarized using descriptive statistics.

Bleeding episodes that were treated with both study and non-study medication will be included in the determination of the number of injections required to resolve the bleeding episode but not in either the average dose per injection or total dose required.

For the above analysis, data from the FAS will be summarized.

7.4.2. Time from Last Injection of rFVIIIFc to a Bleeding Episode

The time (in days) between a spontaneous bleeding episode and the most recent previous prophylaxis injection of rFVIIIFc, will be calculated and summarized using descriptive statistics. Time will be determined in minutes and then converted to days as total minutes divided by 1440. Of note, the reference time for the bleeding episode is the onset of the bleed and not the time treatment for the bleed was first administered. The definition of a new bleeding episode can be found in Section 7.1.1.

The time from the last prophylactic injection to a new spontaneous bleeding episode will be determined on both a per-bleeding episode and per-subject basis. Each evaluable spontaneous bleeding episode will be included as a separate observation in the summary statistics for the per-bleeding episode evaluation. Evaluable bleeding episodes are those for which both a date and time are available for both the onset of the bleeding episode and the previous prophylactic injection. For the per-subject evaluations, times will be averaged across all evaluable spontaneous bleeding episodes per subject and descriptive statistics will be provided for this per-subject average time.

Bleeding episodes that were treated with non-study medication will be included in these analyses, regardless of which treatment was administered first, if all other information needed to calculate the endpoint value is available.

7.4.3. Time Between the First and Second Injection to Treat a Bleeding Episode

In order to characterize the resolution of bleeding episodes treated with rFVIIIFc, the time between the first and second injections to treat a bleeding episode will be determined on both a per-bleeding episode and a per-subject basis.

Per bleeding episode: The time (in hours) between the first and second injections to treat a bleed will be summarized using descriptive statistics across all bleeding episodes, including those with type=Unknown, that required at least 2 injections for resolution.

Per subject: The number of hours between the first and second injections to treat a bleeding episode, as determined for the per-bleeding episode summaries, will be averaged across all evaluable bleeding episodes per subject. Descriptive statistics will be provided for the per-subject average times.

Additionally, the time between the first and second injections to treat a bleed will be summarized per bleeding episode and per subject by type of bleed (spontaneous, traumatic) using descriptive statistics.

Bleeding episodes that were treated with non-study medication will be included in the determination of the time between the first and second injections.

7.4.4. Hemophilia Joint Health Score

Joint assessment will be collected using a modified Hemophilia Joint Health Score (HJHS) for adult subjects and use the HJHS for pediatric subjects.

The Modified HJHS assessment includes the scoring of six joints (left ankle, right ankle, left elbow, right elbow, left knee, right knee) on a scale from 0 to 19 according to the following criteria: swelling, duration, muscle atrophy, crepitus, flexion loss, extension loss, instability, joint pain, and strength. Gait will be scored on a scale from 0 to 2 based on walking and climbing stairs. The total score will be the sum of scores from all 6 joints plus the gait score (range from 0 to 116, with 0 being normal and 116 being the most severe disease).

The HJHS assessment includes the scoring of six joints (left ankle, right ankle, left elbow, right elbow, left knee, and right knee) on a scale from 0 to 20 according to the following criteria: swelling, duration of swelling, muscle atrophy, crepitus of motion, flexion loss, extension loss, joint pain, and strength. Gait will be scored on a scale from 0 to 4 based on the number of skills that are not within the normal limits. The total score will be the sum of scores from all six joints plus the gait score (range from 0 to 124, with 0 being normal and 124 being the most severe disease).

The total and gait scores and change from study 8HA01EXT baseline will be summarized by visit for overall treatment regimen for Safety Analysis Set. The study 8HA01EXT baseline is defined above in Section 5.1.

Modified HJHS and HJHS scoring details are given in Appendix H.

7.5. Endpoints Based on Patient-reported Outcomes

The following patient-reported outcomes will be assessed and data listings will be provided. Analyses involving baseline value will be based on study 8HA01EXT Baseline (as defined above in Section 5.1).

7.5.1. HAEMO-QoL and HAEM-A-QoL

The questionnaires will be analyzed according to the recommendations of the questionnaire authors (see http://www.haemoqol.de). Details of the questionnaire are provided in Appendix C.

The algorithm for deriving the sub scores is given in Appendix C.

The HAEMO-QoL questionnaire for Children and Teenagers aged 13-16 contains 12 sub-grouped sections, which will count as 12 separate sub-scores. Further details on the sub-scores are contained in Appendix C. The following sub-sections make up the 12 sub-scores of the HAEMO-QoL questionnaire:

Time Period	Sub-scores for HAEMO-QoL
During the past month	1. Physical health 2. Feeling 3. View of yourself 4. Family 5. Friends 6. Perceived support 7. Others persons 8. Sports and school 9. Dealing with hemophilia 10. Treatment 11. Future 12. Relationships

The HAEM-A-QoL questionnaire for Adults contains 10 sub-grouped sections, which will count as 10 separate sub-scores. The following sub-sections make up the 10 sub-scores of the HAEM-A-QoL questionnaire:

Time Period	Sub-scores for HAEM-A-QoL
During the past month	1. Physical health 2. Feeling of yourself 3. View 4. Sports and leisure 5. Work and school 6. Dealing with hemophilia 7. Treatment
Recently	8. Future 9. Family planning 10. Partnership and sexuality

As specified in Appendix C, questions will either have been coded or will be re-coded to ensure that high scores represent a low quality of life and low scores represent a high quality of life. These scores are then transformed to produce a Transformed Scale Score (TSS). This score is

scaled, as a percentage, from 0 to 100%, with higher TSS values representing a worst quality of life for each sub-score and total score summary measurement.

For both the HAEMO-QoL and HAEM-A-QoL questionnaires the total scores and individual sub-scores based on the TSS will be summarized for the observed value and change from study 8HA01EXT baseline for the FAS.

7.5.2. Hemo-Sat Patient Satisfaction Scale

A copy of the questionnaire and further details on the subscales and the calculation of the subscores are contained in Appendix F.

As specified in Appendix F, questions will either have been coded or will need to be re-coded to ensure that high scores represent a low satisfaction and low scores represent a high satisfaction. These scores are then transformed to produce a Transformed Scale Score (TSS). This score is scaled as a percentage from 0 to 100% for each sub-score and total score, with higher TSS values representing a worst satisfaction.

The total score and individual subscores based on the TSS will be summarized for the observed response and change from baseline using descriptive statistics for the FAS. A negative change from baseline represents an improvement in satisfaction. Summaries will be at each visit. See Section 5.1.3 for details of when questionnaire results should be excluded from tabulated summaries.

7.5.3. CHO-KLAT

Two forms of the assessment tool were administered for subjects from 8HA02PED, one to the subjects (Child Self-report Questionnaire), and one to the parent/caregiver (Parent/Proxy Questionnaire).

A copy of the questionnaires and details on their scoring are provided in Appendix E. As specified in Appendix E, questions will either have been coded or will need to be re-coded to ensure that high scores represent a high quality of life and low scores represent a low quality of life. These scores are then transformed to produce a Transformed Scale Score (TSS). This score is scaled, as a percentage, from 0 to 100%, with higher TSS values representing a better quality of life.

The total score based on the TSS will be summarized for the observed response and change from study 8HA01EXT baseline using descriptive statistics for subjects ≥5 years old in study 8HA02PED. A positive change from baseline represents an improvement in quality of life. Summaries will be at each visit. See Section 5.1.3 and Appendix E for details of when questionnaire results should be excluded from tabulated summaries.

7.5.4. EQ-5D Youth Questionnaire

The EQ-5D™ is a standardized instrument used to measure health outcome. EQ-5D-Y is a version of this instrument developed for use in children aged 7 to 12 years old.

The questionnaire will be analyzed according to the recommendations of the authors (see www.euroqol.org). EQ-5D-Y consists of 2 pages – a 5 dimension descriptive system and the EQ visual analogue scale. The elements of the questionnaire are provided in Appendix G.

The descriptive system contains 5 categories: mobility; looking after myself; doing usual activities; having pain or discomfort; and feeling worried, sad, or unhappy. Each category has 3 levels of response representing no problems, some problems, and a lot of problems.

The EQ visual analogue scale is a visual scale from 0 to 100 used to record a subject's overall self-rated health state. The subject is asked to mark an 'X' on the scale then record the corresponding number; 0 refers to the worst possible health state, 100 refers to the best possible health state.

The EQ visual analogue scale will be summarized for the observed response and change from study 8HA01EXT baseline using descriptive statistics for children 7 to <12 years of age for the FAS. Subjects for whom the baseline value is zero will be excluded from this analysis. See Section 5.1.3 for details of when questionnaire results should be excluded from tabulated summaries.

7.5.5. EQ-5D-3L Questionnaire

The questionnaire will be analyzed according to the recommendations of the authors (see www.euroqol.org). EQ-5D consists of 2 pages – a 5 dimension descriptive system and the EQ visual analogue scale. A copy of the questionnaire is provided in Appendix D.

The descriptive system contains 5 categories: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. These categories are scored on a scale of 1 to 3, with 1 being the best response, and 3 being the worst response. A total score can also be calculated for the EQ-5D-3L questionnaire. For ease of interpretation, these scores will be transformed into a 0-100 scale by using the following steps:

- Sum all of the sub-category scores (can take values from 5-15) and divide by the maximum possible score overall (3 x 5 categories = 15). If all questions within each sub-category are missed, exclude these from analysis.
- The total score is calculated as: 100 * (subject total score/maximum possible score)

The 5 categories and total will be summarized for the observed response and change from the study 8HA01EXT baseline for the FAS. See Section 5.1.3 for details of when questionnaire results should be excluded from tabulated summaries.

The EQ visual analogue scale is a visual scale from 0-100 to record a respondent's overall self-rated health state. The respondent is asked to mark an 'X' on the scale then record the corresponding number; 0 refers to the worst possible health state, 100 refers to the best possible health state. This will also be presented alongside the 5 dimension descriptive system scores. The EQ visual analogue scale will be summarized for the observed response and change from the study 8HA01EXT baseline for the FAS. See Section 5.1.3 for details of when questionnaire results should be excluded from tabulated summaries.

7.5.6. Health-Economic Parameters

Health-economic assessments consist of the following items based on the time period since the last visit at which they were assessed:

- Number of hospitalizations excluding planned hospitalizations, elective surgery documented at Visit 1, and emergent surgery

- Number of emergency room visits
- Number of physician visits, excluding study visits
- Number of hospitalization days
- Number of days off work, school, day care, or preschool
- Number of days off work for the parent or caregiver

The previous visit for the Visit 1 refers to the previous visit in the parent study where applicable.

These data will be tabulated categorically at each visit for overall treatment regimen for the FAS.

Information collected on the questionnaire relates to both hemophilia and non-hemophilia related events. Thus, in addition to summarizing the hemophilia-related health resource utilization, the utilization for hemophilia- and non-hemophilia related events will be combined and the total summarized for the last 4 assessments listed above.

7.6. Surgery Data

Due to the small overall size of the Surgery Subgroup as described in Section 4.4, efficacy analyses will predominantly be based on assessment of subject data listings.

The following information will be provided in the data listings:

- Dates/times for the various components of the surgical rehabilitation period (hospital admission, surgery, discharge)
- The surgical procedure performed, blood loss, drainage
- Blood products used including details for type of transfusion, date/time administered, and amount given
- Surgeon's/investigator's assessment of hemostatic response to rFVIIIFc
- Dosing during surgery, on the day of surgery, and for the first 14 days post-surgery (Days 1-3, Days 4-14, and Days 1-14)
    - during surgery: number of injections, average dose per injection, and total dose required to maintain hemostasis
    - day of surgery: total dose required to maintain hemostasis
    - post-surgery: total rVIIIFc administered, the total number of injections, and the minimum and maximum intervals of time between injections
- The number of injections required to maintain hemostasis and average daily dose on the day of surgery and for Days 1-3 and Days 4-14 following surgery
- Injections and bleeding episodes during surgery and for the first 14 days following surgery, FVIII levels, reason for injection, nominal dose, hours since the last injection, and if any additional treatment was given to treat the bleed

The following information will be summarized for the FAS:

- Number of injections and mean and total dose per injection required to maintain hemostasis during the major surgical period
- Estimated blood loss during major surgery
- Total rFVIIIFc consumption (IU/kg) per major surgery
- Number of bleeds after surgery per major surgery

In addition, minor surgeries will be summarized and listed where possible in a similar manner for the FAS.

During surgery includes the pre-surgery dose given for the surgery. The day of surgery refers to the calendar day of the surgery and includes the pre-surgery dose given for the surgery, even if it was given on the previous day. Day 1 refers to the day following surgery. The average dose per injection will be determined as the average dose across all injections during the referenced time period. Total dose will be determined as the sum of all doses administered during the referenced time period.

7.6.1. Investigators'/Surgeons' Assessment of Hemostatic Response to Surgery Using the 4-point Bleeding Response Scale

The Investigators'/Surgeons' assessment (using the 4-point surgery response scale detailed in Appendix 2) of the subject's hemostatic response to rFVIIIFc within 24 hours post-surgery will be summarized categorically for all major surgeries for the FAS. Categorically, the number and percentage of surgeries given each rating will be tabulated. Percentages will be based on the number of surgeries for which a response was provided.

The above data will be summarized for both major and minor surgeries in 8HA01EXT.

7.7. Pharmacokinetic Assessments

FVIII activity levels data will be provided in a listing.

8. SAFETY ANALYSIS

Safety data will be summarized for subjects from the parent study or subjects from the parent studies combined along with the overall total. The analysis population for safety analyses is defined in Section 4.3.

Adverse events (AEs) will be summarized for subjects from each parent study and overall for all subjects in study 8HA01EXT, regardless of treatment arm for subjects from studies 997HA301, 997HA307, and 997HA309, age cohort for subjects from study 8HA02PED, and treatment regimen in study 8HA01EXT.

In addition, all data from study 8HA01EXT will be provided in data listings.

8.1. Primary Endpoint

The primary safety endpoint is the occurrence of inhibitor development as determined from the Nijmegen-modified Bethesda assay. A listing of inhibitor test results will be provided.

8.2. Adverse Events

AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes and preferred terms. MedDRA version 15.0 will be used throughout the study. All AEs will be listed.

In general, AEs will be analyzed based on *incidence*, defined as the proportion of subjects who had at least one occurrence of an event out of the number of subjects in the Safety Analysis Set.

All adverse event listings will include the onset and resolution study days relative to 8HA01EXT Study Day 1. AEs that are emergent during a major surgical/rehabilitation period, AEs that are emergent on the day of surgery and AEs that occur during the gap of greater than 7 or 4 days will be flagged. In addition, a separate listing will be provided for AEs that are emergent during a major surgical/rehabilitation period.

AEs occurring during a major surgical/rehabilitation period with an onset date on the day the surgical/rehabilitation period starts or on the day of the surgery will be included in the summaries of the study AEs but excluded from the summaries or listings of AEs occurring during a major surgical/rehabilitation period. Consideration is given to AEs with an onset date at the start of the surgical/rehabilitation period in the event the pre-surgical dose was administered the day before the surgery.

Events of overdose will not be included in the AE summary tables unless they are reported as adverse events.

The algorithm for the determination of AEs that are emergent during a major surgical/rehabilitation period, AEs with an onset date on the day of the surgical/rehabilitation period starts or on the day of the surgery, and AEs that are emergent during a treatment regimen period when an onset date is partially or completely missing is described below.

- If the onset date of an adverse event is present, then the date of onset will be compared with the start/stop dates of the major surgical/rehabilitation period and treatment regimen period to determine whether the adverse event is during a major surgical/rehabilitation

period, on the day of the surgical/rehabilitation period starts or on the day of the surgery, or during a treatment regimen period. If the onset of the adverse event is on the day of the treatment regimen change, then it will be attributed to the previous treatment regimen.

- If the onset day of an adverse event is missing and the onset month and year of the AE are completely within a major surgical/rehabilitation period or a treatment regimen period, then the AE will be attributed to that major surgical/rehabilitation period or that treatment regimen period. For example, the onset of an AE is recorded as 2013-03. A major surgical/rehabilitation period for that subject needs to cover at least from 00:01 on the later date of 2013-03-01 and 8HA01EXT Study Day 1 to 23:59 on the earlier date of 2013-03-31 and the end of his safety period for that AE to be attributed to that major surgical/rehabilitation period. Similarly, if the start and stop time of a treatment regimen do not completely cover the possible range of the onset of AE, then the treatment regimen for that AE will be set to unknown. Regardless of the above, the AE will not be attributed to the day the major surgical/rehabilitation period starts or the day of the major surgery because the exact date is missing.
- If the onset day and month of an adverse event are missing and the onset year of the AE is completely within a major surgical/rehabilitation period or a treatment regimen period, then the AE will be attributed to that major surgical/rehabilitation period or that treatment regimen period. For example, the onset of an AE is recorded as 2013. A major surgical/rehabilitation period for that subject needs to cover at least from 00:01 on the later date of 2013-01-01 and 8HA01EXT Study Day 1 to 23:59 on the earlier date of 2013-12-31 and the end of his safety period for that AE to be attributed to that major surgical/rehabilitation period. Similarly, if the start and stop time of a treatment regimen do not completely cover the possible range of the onset of AE, then the treatment regimen for that AE will be set to unknown. Regardless of the above, the AE will not be attributed to the day the major surgical/rehabilitation period starts or the day of the major surgery because the exact date is missing.
- If the AE onset date is completely missing, the AE will be considered to be outside any major surgical/rehabilitation period and the treatment regimen for that AE will be set to unknown.

8.2.1. Overall Summary of Treatment-emergent Adverse Events

An overall summary of treatment-emergent adverse events (TEAEs) will be provided which tabulates the number and percentage of subjects who experienced a TEAE, related TEAE, treatment-emergent SAE, or treatment-emergent related SAE; the number and percentage of subjects who discontinued treatment or withdrew from the study due to an AE; and the number and percentage of subjects who died. This table will also be presented by subgroup based upon contemporaneous entry compliance of </≥ 80%, as described in Section 6.5.5.3.

AEs that occurred during major surgical/rehabilitation periods will be included in the overall summary of AEs (in the surgery subgroup column) but not in any of the other AE summary tables.

8.2.2. Treatment-emergent Adverse Events

In general, an AE will be regarded as treatment-emergent if it was present prior to receiving the first injection of rFVIIIFc in the parent study and subsequently worsened in severity, or was not present prior to receiving the first injection but subsequently appeared before the subject's last visit on study or the follow-up phone call, whichever came later (or the date of withdrawal/loss to follow-up).

All AEs that occurred on or after the 8HA01EXT Study Day 1 will be considered treatment-emergent in study 8HA01EXT, regardless of the gap between the parent study and study 8HA01EXT. AEs that were treatment-emergent in the parent studies and carried over to study 8HA01EXT without worsening in severity will be considered the same AEs and will not be counted again in study 8HA01EXT.

The incidence of TEAEs will be summarized by system organ class (SOC) and preferred term. Unless specified otherwise, SOCs and preferred terms within each SOC will be presented alphabetically. For the purpose of summarization, a subject is counted once in a SOC or preferred term if the subject reported one or more events in that SOC or preferred term. Unless specified otherwise, percentages will be based on the number of subjects in the Safety Analysis Set.

8.2.3. Adverse Events in Descending Order of Incidence

A table will be provided which displays TEAE preferred terms in descending order of incidence. Only preferred terms will be included in this table (i.e., the display will not include SOCs).

A similar table will be provided for severe TEAEs. AEs for which the assessment of severity is missing will be included in this table.

8.2.4. Severity of Adverse Events

AEs are classified by the Investigator for severity ("Mild", "Moderate", and "Severe"). A summary of TEAEs by system organ class, preferred term, and severity will be presented. AEs with a missing severity will be counted as "Severe" in the summary table. A subject will be counted once for each SOC and preferred term based on the greatest severity within that SOC and preferred term, respectively.

8.2.5. Relationship of Adverse Events to Study Drug

AEs are classified by the Investigator for relationship to study drug ("Not related" and "Related"). A summary of TEAEs by SOC, preferred term, and relationship will be presented. AEs with a missing relationship will be counted as "Related" in the summary table. A subject will be counted once for each SOC and preferred term based on the highest relationship within that SOC and preferred term, respectively.

8.2.6. Serious Adverse Events

Any AE reported as resulting in death, immediate risk of death (life threatening), inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital/anomaly/birth defect will be classified as an SAE by the Investigator. An SAE may also be any other medically important event that, in the opinion of

the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

All SAEs will be listed; treatment-emergent SAEs will be summarized by system organ class and preferred term.

8.2.7. Adverse Events Leading to Treatment Discontinuation or Withdrawal From the Study

AEs leading to treatment discontinuation or withdrawal from the study will be listed. All AEs reported on the AE log for the item "Was the subject terminated from this study due to this AE" with a response of "Yes" or "Action Taken with Study Drug" with a response of "Drug Withdrawn" will be included.

8.2.8. Deaths on Study

A listing of deaths occurring on study 8HA01EXT will be provided.

8.3. Clinical Laboratory Evaluations

Analyses for laboratory data involving baseline value will be based on study 8HA01EXT Baseline (as defined above in Section 5.1).

All summaries will be structured such that the hematology and chemistry tests are presented in the order shown in the tables provided in Section 8.3.1.

All laboratory data will be provided in data listings; abnormal values relative to laboratory normal ranges will be identified. Laboratory evaluations taken during major surgical/rehabilitation periods will be included in the listings and flagged.

8.3.1. Hematology and Chemistry

Hematology measurements that will be collected and listed include white blood cell count (WBC), differential, hemoglobin, hematocrit, and platelet count.

Chemistry measurements that will be collected and listed include electrolytes (sodium, potassium, chloride), glucose, total protein, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) [collected for subjects from study 997HA301 only], blood urea nitrogen (BUN), and serum creatinine.

8.3.1 .1 Change from Study 8HA01EXT Baseline

Hematology and chemistry results at baseline and post baseline visits, along with change from baseline, will be summarized with descriptive statistics for Safety Analysis Set.

8.3.1.2 Shifts

Each subject's laboratory values will be classified according to whether the test result is "low" (below the lower limit of normal [LLN]), "normal" (within the normal range), "high" (above the upper limit of normal [ULN]). Shift tables will be constructed based on both the minimum and maximum post-baseline values for each subject. Data collected from unscheduled visits will be included in the determination of the per subject minimum and maximum values. A separate table will be provided which summarizes the results of the shift tables in which the number and

percentage of subjects with a shift to low (from normal, high, or unknown) and the number of subjects with a shift to high (from normal, low, or unknown) will be tabulated; percentages will be based on the number of subjects at risk. The number at risk for a shift to low (high) is the number of subjects whose baseline value was not low (high), including unknown, who had at least one post-baseline value. Only directions of change indicating a clinical concern will be included in this table summarizing the shifts. The direction of concern is provided in Table 1.

Table 1: Direction of Change Indicating Clinical Concern for Laboratory Tests

Laboratory Test	Direction	Laboratory Test	Direction
Chemistry		Hematology	
Liver		White blood cells	Low and High
ALT/SGPT	High	Lymphocytes	Low and High
AST/SGOT	High	Neutrophils	Low and High
Total bilirubin	High	Monocytes	Low and High
GGT	High	Eosinophils	Low and High
Renal		Basophils	Low and High
Blood urea nitrogen	High	Red blood cells	Low and High
Creatinine	High	Hemoglobin	Low and High
Electrolytes		Hematocrit	Low and High
Sodium	Low and High	Platelets	Low and High
Potassium	Low and High		
Chloride	Low and High		
Other			
Glucose	Low and High		
Total protein	Low and High		

8.3.1.3 Potentially Clinically Significant Laboratory Abnormalities

Abnormal laboratory values will also be evaluated by determining the number and percentage of subjects with at least one potentially clinically significant laboratory abnormality over the course of the study that also represents a worsening from baseline. The potentially clinically significant levels are based on Grade 2 or higher thresholds from the Common Toxicity Criteria for Adverse Events (CTCAE v 4.02 2009) where possible, or were defined by Bioverativ's Safety and Benefit Risk Management group. Subjects who have a post baseline laboratory value that meets the criteria for being potentially clinically significant but do not have a baseline value will be included in the numerator for determining the percentage of subjects with an abnormality. Percentages will be based on the number of subjects with at least one post baseline value for the given laboratory test. Threshold levels for potentially clinically significant laboratory abnormalities are provided in Table 2 (hematology) and Table 3 (chemistry). Data collected from unscheduled visits will be included in this analysis.

Table 2: Threshold Levels for Potentially Clinically Significant Hematology Abnormalities

Subjects from studies 997HA301/997HA307/997HA309		
	Low	High
White blood cells	$<3.0 \times 10^9$/L	$\geq 16 \times 10^9$/L
Lymphocytes	$<0.8 \times 10^9$/L	$>12 \times 10^9$/L
Neutrophils	$<1.5 \times 10^9$/L	$>13.5 \times 10^9$/L
Monocytes	NA	$>2.5 \times 10^9$/L
Eosinophils	NA	$>1.6 \times 10^9$/L
Basophils	NA	$>1.6 \times 10^9$/L
Hemoglobin	≤115 g/L	≥190 g/L
Hematocrit	≤37%	≥60%
Platelet count	$\leq 75 \times 10^9$/L	$\geq 700 \times 10^9$/L
Subjects from study 8HA02PED		
	Low	High
Neutrophils	$<1.5 \times 10^9$/L	NA
Eosinophils	NA	$>1.6 \times 10^9$/L
Hemoglobin	<100 g/L	Increase in >20 g/L above ULN
Hematocrit	<30%	≥60%
Platelet count	$\leq 75 \times 10^9$/L	$\geq 700 \times 10^9$/L

NA = not applicable

Table 3: Threshold Levels for Potentially Clinically Significant Chemistry Abnormalities

Subjects from studies 997HA301/997HA307/997HA309		
	Low	High
Liver		
ALT/SGPT	NA	≥3 × ULN
AST/SGOT	NA	≥3 × ULN
Total bilirubin	NA	≥34.2 µmol/L
Renal		
Blood urea nitrogen	NA	≥10.7 mmol/L
Creatinine	NA	≥176.8 µmol/L
Electrolytes		
Sodium	≤126 mmol/L	≥156 mmol/L
Potassium	≤3 mmol/L	≥6 mmol/L
Chloride	≤90 mmol/L	≥118 mmol/L
Other		
Glucose	≤2.22 mmol/L	≥9.71 mmol/L
Total protein	≤45 g/L	≥100 g/L
Subjects from study 8HA02PED		
	Low	High
Liver		
ALT/SGPT	NA	>3 × ULN

AST/SGOT	NA	>3 × ULN
Total bilirubin	NA	>1.5 × ULN
Renal		
Creatinine	NA	>1.5 × ULN
Electrolytes		
Chloride	≤90 mmol/L	≥118 mmol/L
Other		
Glucose	<3.1 mmol/L	>8.9 mmol/L
Total protein	≤45 g/L	≥100 g/L

NA = not applicable, ULN = upper limit of normal

8.3.2. Inhibitor Development

Inhibitor results of the Nijmegen-modified Bethesda Assay from the central lab will be listed. Results from blood samples collected during surgical/rehabilitation periods for the purpose of determining the presence of an inhibitor will be included.

A positive inhibitor occurs where a subject has a value ≥0.6 Bethesda Units (BU/mL) confirmed on re-testing between 2 and 4 weeks later. Both tests must be performed by the central laboratory.

A "low" titer inhibitor occurs where a subject has a value between 0.6 and <5.0 Bethesda Units (BU/mL) confirmed on re-testing between 2 and 4 weeks later.

A "high" titer inhibitor occurs where a subject has a value ≥5.0 Bethesda Units (BU/mL) confirmed on re-testing within 2 to 4 weeks.

8.3.3 Incidence of Anti-rFVIIIFc Antibodies

The development of anti-rFVIIIFc antibodies will be assessed as the number and percentage of subjects negative throughout the study, positive at any time following study 8HA01EXT Study Day 1, and positive at the final evaluation. Percentages will be based on the number of subjects who are antibody negative prior to study 8HA01EXT baseline and have at a post baseline antibody evaluation for the referenced time point or time interval.

Results from blood samples collected during surgical/rehabilitation periods for the purpose of determining the presence of anti-rFVIIIFc antibodies will be included in this analysis.

In addition to a listing of all anti-rFVIIIFc antibody results, a separate listing of all results from subjects with at least one positive outcome during the study, including at baseline, will be provided.

8.4. Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse, respiratory rate, and oral temperature) will be summarized for the observed values and change from baseline using descriptive statistics for the Safety Analysis Set.

The number and percentage of subjects with clinically relevant post-baseline abnormalities will be presented. The criteria for clinically relevant post-baseline abnormalities are shown below in Table 4.

Table 4 Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°C and an increase from pre-dosing of at least 1°C
Pulse	>120 beats per minute post-baseline, or
	an increase from pre-dosing of more than 20 beats per minute, or
	<50 beats per minute post-baseline, or
	a decrease from pre-dosing of more than 20 beats per minute
Systolic Blood Pressure	>180 mmHg post-baseline, or
	an increase from pre-dosing of more than 40 mmHg, or
	<90 mmHg post-baseline, or
	a decrease from pre-dosing of more than 30 mmHg
Diastolic Blood Pressure	>105 mmHg post-baseline, or
	an increase from pre-dosing of more than 30 mmHg, or
	<50 mmHg post-baseline, or
	a decrease from pre-dosing of more than 20 mmHg

A listing of all vital signs (added height and weight) will be provided, including from unscheduled visits and during surgical/rehabilitation periods. Vital signs collected during surgical/rehabilitation periods as well as those occurring on the day of surgery will be flagged in this listing.

9. Sensitivity Impact Assessment

As proposed under the MHRA CAPA commitment, an analysis will be performed to assess the impact of the EPD query process and addition of manually created records on the results of study 8HA01EXT. The analysis will include summary tables that will be re-run plus any additional summary tables or listings required for inclusion in the final clinical study report (CSR).

Background

Subject recorded diary data was queried via a defined process which originally required confirmation with the subject of **all** changes. Subsequently, it was identified that this did not occur in all cases nor was this actually necessary for all types of change. In 2014, it was agreed that only certain categories of changes required subject confirmation, and a process implemented to ensure adequate documentation to support those changes was available. After a subsequent MHRA audit in 2015, further consideration was given to the timing of changes relative to the actual data generation, reliable subject recall period, and still lack of appropriate documentation to support changes in all cases. Therefore, taking into consideration these findings and industry standards to limit changes of subject reported data, the query process was updated to **only allow changes defined as not requiring subject confirmation**. Although changes classified as SVC/L60 did not require subject confirmation (as agreed with MHRA in 2014), these changes will no longer be made directly into the data, but will be applied via a programmatic data convention (details described in Section 5.4).

The Total Query Report (TQR) documents all changes to the EPD data. The changes in this report were classified according to a pre-defined list (see table below).

Code	Description	Requires subject confirmation
LN	Minor lot # change (addition/deletion of spaces or hyphens) and Major lot # change (any other changes to lot #)	N
D/EPD	Duplicate entry in EPD by subject - deleted	Y
D/CRF	Entry in EPROLOG is also in CRF/INFORM as in-clinic dose	N
Dose	Vials added or removed	Y
SVC	Single vials combined - entered as separate injections in error	Y
SVC/L60	Single vials combined - entered as separate injections in error – injection time range for combined records is $\leq$60 mins	To be applied via programmatic data convention during analysis as described in Section 5.4
Error	Subject entered in error - entry deleted	Y
DTOI	Date and/or time of injection corrected	Y
Pre-Fc	Entries deleted as prior to first dose with Fc (not required per protocol)	N
Train	Entries deleted as training/prior to first dose with Fc (not required per protocol)	N
Test subject	Subject does not exist - entries deleted	N

Code	Description	Requires subject confirmation
Inj Reason	Reason of injection changed (other than routine prophylaxis or other to surgical prophylaxis if a confirmed minor/major surgery or procedure is capture in the eCRF during the defined surgical period or date of procedure; or from new bleed to follow up)	Y
Inj Reason Surgery	Injection reason from routine prophylaxis or other to surgical prophylaxis	N
BLD LOC	Change in Bleed Location	Y
BLD TYP	Change in Bleed Type	Y
BLD SYM	Change in Bleed Symptoms	Y
DTOB	Date and/or time of bleed corrected	Y
Activity	Change in Physical Activity question	Y
TRT SD	Amendment to Treat with Study Drug item: "Did you inject with rFVIIIFc (Study Drug)?"	Y
TRT BLD	Amendment to Treat Bleed item: "How did the bleed respond to injection on ..."	Y
Abandon	Query request was raised but then cancelled by site	N
In-clinic administration	In-clinic administration entered in EPD and corrected in reference to source records	N
NBTFU	Injection to treat the bleed is < 72 h of the previous injection to treat the existing bleed New bleed deleted, follow up inj to existing bleed added (per protocol definition)	N
Tx Arm/Reg	Change in treatment arm or regimen	N
ADMIN	Changes made by site to data fields that the site would have entered originally and/or are administrative. E.g. study name or data entered into an incorrect field and corrected, data entered that is not required, expiry date of IMP extended, data field changes that are duplicated due to multiple site staff involved in the query process or similar, correction of injection reason related to treatment arm, e.g. routine prophylaxis to weekly dose for subjects on a weekly regimen	N

In certain circumstances, where subjects could not enter records directly into the EPD for any reason, records were requested to be created manually by the site according to a pre-defined documented process which included SDV by CRA. However, it was subsequently identified that confirmation of SDV could not be provided. Records were re-SDVed at site to determine whether source was available, or whether contemporaneous documentation of confirmation with the subject was available. (*Not discussed further in this SAP*).

For the impact assessment, all data record changes requiring subject confirmation will be set back to the original values. Although changes classified as SVC/L60 did not require subject confirmation (as agreed with MHRA in 2014), these changes will no longer be made directly into

the data, but will be applied via a programmatic data convention (described in Section 5.4). Manually created data without complete SDV of the record versus a paper diary will be considered unsupported by SDV at site, and will be removed for the purpose of the impact assessment. SDTM and ADAM datasets will be re-created and certain statistical analyses re-run. Endpoints covered under the impact assessment include:

- exposure
- annualized number of bleeding episodes per subject (ABR)
- subjects assessment of response to treatment with rFVIIIFc for bleeding episodes
- number of injections and dose per injection of rFVIIIFc required to resolve a bleeding episode
- prophylactic dose and dosing interval

9.1 Data Record Changes

A summary of the number and percentage of data record changes and manually created records by record and subject will be produced, overall and by change classification, and whether contemporaneous confirmation with subject was required.

In addition, a listing of the data record changes (to include value pre-change, value post-change, change classification and contemporaneous subject confirmation flags) will be produced.

9.2 Existing Outputs to be Re-run

The summary tables will be regenerated based on updated ADAM datasets are shown in Table 5.

Table 5: Summary Tables Rerun With the Updated Datasets

Outputs	Summary Table titles	Program file name
Disposition	Disposition	T-DISPOSITION.SAS
Exposure	Summary of exposure	T-EX-SUM.SAS.SAS
	Summary of prophylactic dose (IU/kg)	T-EX-PROPHY-DOSE.SAS
	Summary of prophylactic dose and interval	T-EX-PROPHY-DOSE-INT.SAS
ABR	Summary of annualized bleeding rate	T-ABR-SUM.SAS
Subject response to treatment of bleed	Summary of subject's assessment of response to rFVIIIFc injections for the treatment of bleeding episodes	T-SUBJ-ASSESS-RESP-BLD.SAS

Injections and dose required for resolution of a bleeding episode	Summary of number of injections required for resolution of a bleeding episode	T-INJ-RES-BLD.SAS
Injections and dose required for resolution of a bleeding episode	Summary of dose (IU/kg) of rFVIIIFc for resolution of bleeds	T-DOSE-RES-BLD.SAS

9.3 New Outputs to be Created

Additional listings that are required to support the re-run of existing summary tables for the impact assessment will be created.

The following by subject listings will be created:

- Listing of derived bleeding and injection endpoints per subject – from original and impact assessment
- Listing of dose endpoints – from original and impact assessment
- Listing of exposure – from original and impact assessment

The following listings *may be* created if the results of the impact analysis require further investigation at a bleed or injection level:

- Listing of derived bleeding endpoints based on individual bleeding episodes – from impact assessment
- Listing of injections to treat a bleed – from impact assessment

10. REFERENCES

Bolton-Maggs P, Pasi J. Haemophilias A and B. Lancet. 2003;361:1801–09.

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Mannucci PM, Tuddenham EGD. The hemophiliac: from royal genes to gene therapy. N Engl J Med. 2001;344:1773-1779.

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Rodriguez-Merchan EC. Management of musculo-skeletal complications of hemophilia. Semin Thromb Hemost. 2003;29:87-96.

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11. INDEPENDENT DATA SAFETY MONITORING COMMITTEE

There will be no independent data safety monitoring committee for this study.

LIST OF TABLES, LISTINGS, AND FIGURES

List of Tables (Table titles are suggested. If appropriate, table titles may change during their creation.)

Health Score (HJHS)

Subjects from studies 997HA301/997HA307/997HA309 combined:

Summary of subjects attending each visit
Summary of demographic and baseline characteristics
Summary of medical and surgical history
Summary of concomitant medications
Summary of major protocol deviations
Summary of major protocol deviations based one EPD data in the original pre-change state
Summary of exposure
Summary of exposure by EPD entry compliance
Summary of last prescribed dose and dosing frequency
Summary of changes in study 8HA01EXT treatment regimens
Summary of prophylactic dose (IU/kg)
Summary of prophylactic dosing interval
Summary of annualized rFVIIIFc consumption (IU/kg)
Summary of bleeding episodes
Summary of annualized bleeding rate
Summary of annualized bleeding rate by type of bleeds
Summary of annualized bleeding rate by location and type of bleeds
Summary of annualized bleeding rate by the presence of target joints at screening in parent study
Summary of annualized bleeding rate by EPD entry compliance
Summary of subject's assessment of response to rFVIIIFc injections for the treatment of bleeding episodes
Summary of number of injections required for resolution of a bleeding episode
Summary of dose (IU/kg) of rFVIIIFc for resolution of bleeds
Summary of number of days from the last prophylaxis injection to a spontaneous bleeding episode
Summary of time (hours) between first and second injection to treat a bleeding episode
Summary of time (hours) between first and second injection to treat a bleeding episode by type of bleed

Subjects from study 8HA02PED:

Summary of subjects attending each visit
Summary of demographic and baseline characteristics
Summary of medical and surgical history
Summary of concomitant medications
Summary of major protocol deviations
Summary of major protocol deviations based one EPD data in the original pre-change state
Summary of exposure
Summary of exposure by ePD entry compliance
Summary of last prescribed dose and dosing frequency
Summary of changes in study 8HA01EXT treatment regimens
Summary of prophylactic dose (IU/kg)
Summary of prophylactic dosing interval
Summary of annualized rFVIIIFc consumption (IU/kg)
Summary of bleeding episodes

Summary of annualized bleeding rate
Subjects from study 8HA02PED: Summary of annualized bleeding rate by type of bleeds
Subjects from study 8HA02PED: Summary of annualized bleeding rate by location and type of bleeds
Subjects from study 8HA02PED: Summary of annualized bleeding rate by the presence of target joints at screening in parent study
Subjects from study 8HA02PED: Summary of annualized bleeding rate by ePD entry compliance
Summary of subject's assessment of response to rFVIIIFc injections for the treatment of bleeding episodes
Summary of number of injections required for resolution of a bleeding episode
Summary of dose (IU/kg) of rFVIIIFc for resolution of bleeds
Summary of results and change from study 8HA01EXT baseline: CHO-KLAT total score from the Child Self-report Questionnaire
Summary of results and change from study 8HA01EXT baseline: CHO-KLAT total score from the Parent/Proxy Questionnaire
Summary of results and change from study 8HA01EXT baseline: Hemo-Sat total score and subscores
Summary of EQ-5D-Y descriptive system
Summary of results and change from study 8HA01EXT baseline: EQ-5D-Y visual analogue scale
Summary of hemophilia-related health-economic parameters
Summary of health economic parameters for all physician and emergency room visits
Summary of results and changes from study 8HA01EXT: Hemophilia Joint Health Score (HJHS)

Overall groups of subjects in 8HA01EXT (as described in Section 5.1):
Summary of compliance for the treatment of bleeding episodes
Summary of prophylactic dose compliance
Summary of prophylactic dosing interval compliance
Summary of prophylactic compliance
Summary of EPD entry compliance
Overall summary of rFVIIIFc treatment-emergent adverse events
Summary of rFVIIIFc treatment-emergent adverse events by preferred term in descending order of incidence
Summary of rFVIIIFc treatment-emergent adverse events by relationship to treatment
Summary of rFVIIIFc treatment-emergent serious adverse events
Summary of anti-rFIIIVFc antibodies
Surgery subgroup – Summary of Investigators'/Surgeons' assessment of subjects' hemostatic response to rFVIIIFc post major surgery
Surgery subgroup – Number of injections and dose required to maintain hemostasis during major surgery
Surgery subgroup - Estimated total blood loss during major surgery
Surgery subgroup – Total rFVIIIFc consumption (IU/kg) per major surgery
Surgery subgroup - summary of number of bleeds after surgery per major surgery
Summary of Investigators'/Surgeons' assessment of subjects' hemostatic response to rFVIIIFc post minor surgery
Number of injections and dose required to maintain hemostasis during minor surgery

Estimated total blood loss during minor surgery
Total rFVIIIFc consumption (IU/kg) per minor surgery
Summary of number of bleeds after surgery per minor surgery
Summary of laboratory results and change from study 8HA01EXT baseline: Hematology
Shifts from study 8HA01EXT baseline to minimum/maximum post-baseline value for laboratory results: Hematology
Summary shifts from study 8HA01EXT baseline to minimum/maximum post-baseline value for laboratory results: Hematology
Summary of potentially clinically significant laboratory abnormalities: Hematology
Summary of laboratory results and change from study 8HA01EXT baseline: Blood Chemistry
from study 8HA01EXT baseline to minimum/maximum post-baseline value for laboratory results: Blood Chemistry
Summary of shifts from study 8HA01EXT baseline to minimum/maximum post-baseline value for laboratory results: Blood Chemistry
Summary of potentially clinically significant laboratory abnormalities: Blood Chemistry
Summary of vital sign results and change from study 8HA01EXT baseline
Summary of clinical abnormalities from study 8HA01EXT baseline in vital signs

List of Listings (Listing titles are suggested. If appropriate, listing titles may change during their creation.)

Listing of subjects with large gap between the parent study and study 8HA01EXT
Listing of subject disposition
Listing of major and minor protocol deviations
Listing of major and minor protocol deviations based one EPD data in the original pre-change state
Listing of demographic and baseline characteristics
Listing of medical and surgical history
Listing of prior and concomitant medications
Listing of medications taken after the End of Study Visit
Listing of other therapy or concomitant procedures
Listing of prescribed dose and dosing regimen changes
Listing of the Investigator's classification of bleeding episodes which differed from the subject's/caregiver's classification
Listing of weight
Listing of all injections and treated bleeding episodes
Listing of derived bleeding endpoints based on individual bleeding episodes
Listing of derived bleeding and injection endpoints based on subjects
Listing of compliance in treatment of bleed
Listing of exposure
Listing of injections to treat a bleed
Listing of the by-subject summary of the assessment of response to rFVIIIFc for the treatment of bleeding episodes
Listing of dose and consumption endpoints
Listing of the number of bleeding episodes during the efficacy period
Listing of physician's assessment of the subject's global response to his treatment regimen
Listing of major surgery information – hospitalization data

Listing of major surgery information – blood loss
Listing of major surgery information – dosing during and for the first 14 days post-surgery
Listing of major surgery information – transfusions and surgeon's assessment of hemostatic response to rFVIIIFc
Listing of minor surgery information – hospitalization data
Listing of minor surgery information – blood loss
Listing of minor surgery information – dosing during and on the day of surgery
Listing of minor surgery information – transfusions and surgeon's assessment of hemostatic response to rFVIIIFc
Listing of injections and bleeding episodes during and for the first 14 days following major surgery
Listing of FVIII activity levels
Listing of adverse events
Listing of adverse events reported during major surgical/rehabilitation periods
Listing of serious adverse events
Listing of adverse events leading to discontinuation of treatment and/or the study
Listing of adverse events reported in study 8HA01EXT that started before 8HA01EXT Study Day 1 but were not reported in the parent study
Listing of deaths
Listing of laboratory normal ranges
Listing of laboratory values: Hematology (WBC and differential, absolute count)
Listing of laboratory values: Hematology (WBC and differential [%])
Listing of laboratory values: Hematology (red blood cell parameters and platelet count)
Listing of abnormal laboratory values based on the normal range: Hematology
Listing of abnormal laboratory values based on potentially clinically significant abnormalities: Hematology
Listing of laboratory values: Blood Chemistry (liver and renal parameters)
Listing of laboratory values: Blood Chemistry (electrolytes and other parameters)
Listing of abnormal laboratory values based on the normal range: Blood Chemistry
Listing of abnormal laboratory values based on potentially clinically significant abnormalities: Blood Chemistry
Listing of laboratory values: Inhibitor results
Listing of laboratory values: Anti-rFVIIIFc antibodies
Listing of vital sign measurements
Listing of abnormal findings from physical examination
Listing of CHO-KLAT questionnaire (Part 1 of 4)
Listing of CHO-KLAT questionnaire (Part 2 of 4)
Listing of CHO-KLAT questionnaire (Part 3 of 4)
Listing of CHO-KLAT questionnaire (Part 4 of 4)
Listing of CHO-KLAT total score
Listing of Hemo-Sat questionnaire (Ease and convenience)
Listing of Hemo-Sat questionnaire (Efficacy, Burden, General satisfaction)
Listing of Hemo-Sat questionnaire (Specialist/Nurses, Center/Hospital)
Listing of Hemo-Sat total score and sub-scores
Listing of EQ-5D-Y descriptive system
Listing of HAEMO-QoL questionnaire (Part x of 6) - Children and Teenagers aged 13-16

Listing of HAEMO-QoL questionnaire (Total and sub-scores) - Children and Teenagers aged 13-16
Listing of HAEM-A-QoL questionnaire (Part x of 2) - Adults
Listing of HAEM-A-QoL total score and sub-score - Adults
Listing of EQ-5D-L descriptive system
Listing of hemophilia-related health-economic parameters

Sensitivity Impact Assessment (Tables and Listings):
Summary of data record changes by classification and contemporaneous subject confirmation
Listing of data record changes
Listing of derived bleeding and injection endpoints per subject – from original and impact assessment
Listing of dose endpoints – from original and impact assessment
Listing of exposure – from original and impact assessment
Listing of derived bleeding endpoints based on individual bleeding episodes – from impact assessment
Listing of injections to treat a bleed – from impact assessment
Disposition – from impact assessment
Summary of exposure – from impact assessment
Summary of prophylactic dose (IU/kg) Prophylactic dose and interval – from impact assessment
Summary of annualized bleeding rate – from impact assessment
Summary of subject's assessment of response to rFVIIIFc injections for the treatment of bleeding episodes - – from impact assessment
Summary of number of injections required for resolution of a bleeding episode - – from impact assessment
Summary of dose (IU/kg) of rFVIIIFc for resolution of bleeds - – from impact assessment

Data to be Provided in Listings Upon Request

None

List of Figures

None

APPENDIX A. SUBJECT'S ASSESSMENT OF RESPONSE TO TREATMENT OF BLEEDING

Using the eDiary, each subject or the subject's caregiver will rate the treatment response to any bleeding episode using the following 4-point scale (excellent, good, moderate, or none). This assessment is to be made approximately 8 to 12 hours from the time the injection was given to treat the bleeding episode and prior to any additional doses of rFVIIIFc given for the same bleeding episode. In this study, a bleed will be defined as follows: a bleeding episode starts from the first sign of a bleed and ends no more than 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, are considered the same bleed. Any injection to treat the bleed, taken more than 72 hours after the preceding one, will be considered the first injection to treat a new bleed at the same location. Any bleeding at a different location is considered a separate bleed regardless of time from last injection. Response could also be assessed by the Physician for those subjects who were treated in the hospital with rFVIIIFc for major bleeds or post-surgery until discharge from the hospital.

- Excellent: Abrupt pain relief and/or improvement in signs of bleeding within approximately 8 hours after the initial injection
- Good: Definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an injection, but possibly requiring more than one injection after 24 – 48 hours for complete resolution
- Moderate: Probable or slight beneficial effect within 8 hours after the initial injection **and** requires more than one injection
- None: No improvement, or condition worsens within approximately 8 hours after the initial injection

The following evaluations will determine the level of hemostasis achieved with rFVIIIFc treatment during surgery:

- Number of injections and dose per injection required to maintain hemostasis during the surgical period
- Estimated blood loss during surgery (intra-operative period)
- Number and type of blood component transfusions required during surgery

APPENDIX B. SURGERY RESPONSE SCALE

This surgery scale is used for the investigators'/surgeons' assessments of response to surgery with rFVIIIFc treatment.

Excellent: intra-operative and postoperative blood loss similar to (or less than) a person without hemophilia.

- No extra doses of rFVIIIFc needed **AND**
- Blood component transfusions required are similar to a person without hemophilia

Good: intra-operative and/or postoperative bleeding slightly increased over expectations for a person without hemophilia, but the difference is not clinically significant.

- Intra-operative blood loss no more than expected for a person without hemophilia **AND**
- No extra doses of rFVIIIFc needed **AND**
- Blood component transfusions required are similar to a person without hemophilia

Fair: intra-operative and/or postoperative blood loss is increased over expectation for a person without hemophilia and additional treatment is needed.

- Intra-operative blood loss greater than expected for a person without hemophilia **OR**
- Extra dose of rFVIIIFc factor needed **OR**
- Increased blood component transfusion requirement

Poor/none: significant intra-operative and/or postoperative bleeding that is substantially increased over expectations for a person without hemophilia, requires intervention, and is not explained by a surgical/medical issue other than hemophilia

- Intra-operative blood loss greater than for a person without hemophilia **OR**
- Unexpected hypotension or unexpected transfer to intensive care unit due to bleeding **OR**
- Substantially increased blood component transfusion requirement

APPENDIX C. SCORING ALGORITHM FOR HAEM-A-QOL AND HAEMO-QOL

Per the algorithm on **http://www.haemoqol.de/manual.htm**, to correctly score the questionnaires, each version has to be identified and the appropriate scoring list has to be selected. Basically high score represent low quality of life and scoring involves the following steps:

1. Assigning numbers to the response scale, which is applicable to both age groups (children and teenagers aged 13-16 and adults>16)

1= never, 2=rarely, 3=sometimes, 4=often, 5=all the time

For negatively worded items, the above classification can be applied in which higher values represent a lower quality of life. For positively worded items, the score has to be recoded (see below).

2. Recoding positively worded items

Positively worded items in the subscales table have to be recoded so that numeric values assigned are reversed:

1=all the time, 2=often, 3=sometimes, 4=rarely, 5= never

By recoding, high scores in positively worded items reflect not higher but lower quality of life. The then unidirectional values can subsequently be added to yield the summed scores according to the Scoring list for the respective questionnaire.

3. Producing the Raw score

A Raw subscale score is produced by summing up all items within a subscale. Its range lies between the lowest possible (number of items (n) x 1) and highest possible (number of items (n) x 5) value of the respective scale.

The Raw total score is produced by the addition of all items (instead of the subscale items only) of the questionnaire (again paying attention to the recoding procedure – see steps 1 and 2).

4. Transferring a raw score to a Standardized score

A Standardized score is produced by dividing the raw score by the number of items in the sub scale or total. This allows comparison between subscales.

5. Transferring a raw score to a Transformed Score between 0 and 100

Creating a transformed score makes it possible to express the score as a percentage between the lowest (0) and the highest (100) possible value. To obtain the transformed score the following transformation rule has to be applied:

Transformed score= 100 x ((raw score – minimal possible raw score) / possible range of raw scores) where:

- minimal possible raw score = number of questions answered × 1
- maximal possible raw score = number of questions answered × 5
- possible range of raw scores = maximum possible raw score - minimal possible raw score

Example: A raw score of 20 on the "Physical Health" Scale is to be transformed:

- when all 7 questions were answered:
  - minimal possible score=7
  - maximal possible score=35
  - range of scores=28
  - TSS=20-7/28 = 46.4
- when 6 of the 7 questions were answered:
  - minimal possible score=6
  - maximal possible score=30
  - range of scores=24
  - TSS=20-6/24 = 58.3

Transformed scores can be produced from raw subscale and raw total scores.

The total transformed score will be presented in outputs.

6. Presentation of scores

The transformed scores for subscale and total will be presented in the outputs.

7. Subscales

The following sub score categories are included for the HAEMO-QoL (Children and Teenagers aged 13-16) questionnaire:

Time Period	Sub-scores for HAEMO-QoL	No. of questions	No. of non-missing items required to calculate subscale
During the past month	1. Physical health	7	6
	2. Feeling	8	6
	3. View of yourself	10	8
	4. Family	8	6
	5. Friends	4	3
	6. Perceived Support	4	3
	7. Other person	6	5
	8. Sports and School	9	7
	9. Dealing with Hemophilia	7	6
	10. Treatment	8	6
	11. Future	4	3
	12. Relationships	2	2
	Total Score	77	63

The following sub score categories are included for the HAEMO-A-QoL (Adults) questionnaire:

Time Period	Sub-scores for HAEM-A-QoL	No. of questions	No. of non-missing items required to calculate subscale
During the past month	1. Physical Health	5	4
	2. Feeling	4	3
	3. View of yourself	5	4
	4. Sports and leisure	5	4
	5. Work and school	4	3
	6. Dealing with hemophilia	3	3
	7. Treatment	8	6
Recently	8. Future	5	4
	9. Family planning	4	3
	10. Partnership and sexuality	3	3
	Total Score	46	38

8. Sub score Items

Provided below is a copy of both questionnaires. Items are highlighted when they require re-coding as detailed in point 2 above.

HAEMO QoL Child and Teen Questionnaire

[III,kids,long] – CIII-HAEMO-QOL-USA/English –Final Version-29 Jun 07

HAEMO - QOL

Questionnaire for Children and Teenagers	Kids' long Version	age: 13-16

Hello there!

We would like to find out how you have been feeling during the past weeks,

so we have worked out a few questions that we would like you to answer.

This questionnaire was designed for teenagers with hemophilia.

⇨ Please read each question carefully.

⇨ Think about how things have been for you over the past weeks.

⇨ Choose the answer that fits you best and put an "X" in the appropriate box.

There are no right or wrong answers. It's what <u>you</u> think that matters.

For example:	never	rarely	some-times	often	all the time
During the past 7 days, I felt like eating ice cream	☐	☐	☐	☒	☐

Date of completion: |__|__|__|__|__|__|
(month/ day/ year)

Country: |__|__|

We would like to find out about your physical health...

	During the past 7 days...	never	rarely	some-times	often	all the time
1.	... I felt ill	☐	☐	☐	☐	☐
2.	... I was in pain	☐	☐	☐	☐	☐
3.	... I was tired and worn-out	☐	☐	☐	☐	☐
4.	... I felt strong and full of energy	☐	☐	☐	☐	☐
5.	... I was afraid that my illness might get worse	☐	☐	☐	☐	☐

... then about how you've been feeling in general...

	During the past 7 days...	never	rarely	some-times	often	all the time
1.	... I had fun and laughed a lot	☐	☐	☐	☐	☐
2.	... I was bored	☐	☐	☐	☐	☐
3.	... I felt alone	☐	☐	☐	☐	☐
4.	... I felt scared or unsure of myself	☐	☐	☐	☐	☐
5.	... I was sad because of my illness	☐	☐	☐	☐	☐

... and how you have been feeling about yourself.

	During the past 7 days...	never	rarely	some-times	often	all the time
1.	... I took pride in myself	☐	☐	☐	☐	☐
2.	... I felt on top of the world	☐	☐	☐	☐	☐
3.	... I felt content with myself	☐	☐	☐	☐	☐
4.	... I had lots of good ideas	☐	☐	☐	☐	☐
5.	... I was able to cope well with my illness	☐	☐	☐	☐	☐

The next questions are about your family...

	During the past 7 days...	never	rarely	some-times	often	all the time
1.	... I got along well with my parents	☐	☐	☐	☐	☐
2.	... I felt fine at home	☐	☐	☐	☐	☐
3.	... we argued at home	☐	☐	☐	☐	☐
4.	... I felt restricted by my parents	☐	☐	☐	☐	☐
5.	... my parents treated me like a baby because of my illness	☐	☐	☐	☐	☐

... and then about your friends.

	During the past 7 days...	never	rarely	some-times	often	all the time
1.	... I did things together with my friends	☐	☐	☐	☐	☐
2.	... I was popular with my friends	☐	☐	☐	☐	☐
3.	... I got along well with my friends	☐	☐	☐	☐	☐
4.	... I felt different from other people	☐	☐	☐	☐	☐
5.	... I did not want others to notice my illness	☐	☐	☐	☐	☐

Now, we would like to find out about school.

	During the past 7 days...	never	rarely	some-times	often	all the time
1.	... doing my schoolwork was easy	☐	☐	☐	☐	☐
2.	... I found school interesting	☐	☐	☐	☐	☐
3.	... I worried about my future	☐	☐	☐	☐	☐
4.	... I worried about getting bad marks or grades	☐	☐	☐	☐	☐
5.	... I missed something at school because of my illness	☐	☐	☐	☐	☐

NOW WE WOULD LIKE TO ASK YOU SEVERAL QUESTIONS ABOUT YOUR HEMOPHILIA

Here we would like to find out about your **BLEEDS** (JOINT BLEEDS)

1.	How frequent were your bleeds in the past month?				
	☐ no bleeds	☐ 1	☐ 2	☐ more than 2	How many?___

The following questions should only be answered if you had bleeds.

2.	How much were you troubled by bleeds during the past month?				
	☐ not at all	☐ a little	☐ moderately	☐ a lot	
3.	How severe were your bleeds during the past month? (If you had several bleeds, please answer for the most severe bleed.)				
	☐ slight	☐ moderate	☐ severe	☐ very severe	
4.	Did you feel a strange sensation in your joints before you had a bleed?				
	☐ never	☐ rarely	☐ sometimes	☐ often	☐ always
5.	Did you have to stay quiet (e.g., lie in bed) when you had bleeds?				
	☐ never	☐ rarely	☐ sometimes	☐ often	☐ always
6.	When you had bleeds, did you inform your parents immediately?				
	☐ never	☐ rarely	☐ sometimes	☐ often	☐ always

We would like to find out who gave you your **INJECTIONS**

	In the past month...	never	rarely	some-times	often	all the time
1.	... I injected myself	☐	☐	☐	☐	☐
2.	... my mother injected me	☐	☐	☐	☐	☐
3.	... my father injected me	☐	☐	☐	☐	☐
4.	... a nurse injected me	☐	☐	☐	☐	☐
5.	... a doctor injected me	☐	☐	☐	☐	☐

Here we would like to find out about hemophilia and your **PHYSICAL HEALTH**

	In the past month...	never	rarely	some-times	often	all the time
1.	... my swellings hurt	☐	☐	☐	☐	☐
2.	... I had pain in my joints	☐	☐	☐	☐	☐
3.	... it was painful for me to move	☐	☐	☐	☐	☐
4.	... my joints felt stiff	☐	☐	☐	☐	☐
5.	... it was difficult for me to move my arms or legs	☐	☐	☐	☐	☐
6.	... I had difficulty walking as far as I wanted to	☐	☐	☐	☐	☐
7.	... I was afraid of hurting myself	☐	☐	☐	☐	☐

and now about how you have been **FEELING** because of your hemophilia

	In the past month...	never	rarely	some-times	often	all the time
1.	... I was in a bad mood because of my hemophilia	☐	☐	☐	☐	☐
2.	... I was sad because of my hemophilia	☐	☐	☐	☐	☐
3.	... my hemophilia was a burden (real problem) for me	☐	☐	☐	☐	☐
4.	... my hemophilia made me angry	☐	☐	☐	☐	☐
5.	... I was worried because of my hemophilia	☐	☐	☐	☐	☐
6.	... I felt lonely because of my hemophilia	☐	☐	☐	☐	☐
7.	... I was afraid of bleeds	☐	☐	☐	☐	☐
8.	... I felt excluded by my friends	☐	☐	☐	☐	☐

How does hemophilia affect your **VIEW OF YOURSELF**?

	In the past month...	never	rarely	some-times	often	all the time
1.	... I envied healthy boys my age	☐	☐	☐	☐	☐
2.	... I felt physically weaker than other boys	☐	☐	☐	☐	☐
3.	... I felt as well as other boys my age	☐	☐	☐	☐	☐
4.	... I felt comfortable with my body	☐	☐	☐	☐	☐
5.	... hemophilia made my life more difficult	☐	☐	☐	☐	☐
6.	... I was happy even with my hemophilia	☐	☐	☐	☐	☐
7.	... I felt embarrassed about my hemophilia	☐	☐	☐	☐	☐
8.	... I had difficulty doing things with other kids my age	☐	☐	☐	☐	☐
9.	... I was unable to do as much with my friends because of my hemophilia	☐	☐	☐	☐	☐
10.	... I felt healthy even with my hemophilia	☐	☐	☐	☐	☐

Note: Questions 3, 4, 6 and 10 are positively worded and are recoded so that numeric values assigned are reversed:

1=all the time, 2=often, 3=sometimes, 4=rarely, 5= never

The next questions are about hemophilia and your **FAMILY**

	In the past month...	never	rarely	some-times	often	all the time
1.	... I was treated differently by my family because of my hemophilia	☐	☐	☐	☐	☐
2.	... my mother protected me too much	☐	☐	☐	☐	☐
3.	... my father protected me too much	☐	☐	☐	☐	☐
4.	... my parents criticized me when I hurt myself	☐	☐	☐	☐	☐
5.	... my parents didn't allow me to do certain things because of my hemophilia	☐	☐	☐	☐	☐
6.	... there were problems at home because of my hemophilia	☐	☐	☐	☐	☐
7.	... I felt I was causing my family trouble because of my hemophilia	☐	☐	☐	☐	☐
8.	... my parents had less free time or had to miss work because they had to look after me	☐	☐	☐	☐	☐

and then about hemophilia and your **FRIENDS**

	In the past month...	never	rarely	some-times	often	all the time
1.	... I was able to talk to my friends about my hemophilia	☐	☐	☐	☐	☐
2.	... my best friend cared about how I was feeling	☐	☐	☐	☐	☐
3.	... there was a best friend that I felt very close to	☐	☐	☐	☐	☐
4.	... my friends took care of me when I felt bad	☐	☐	☐	☐	☐

Note: Questions 1 to 4 of the FRIENDS subscale are positively worded and are recoded so that numeric values assigned are reversed:

1=all the time, 2=often, 3=sometimes, 4=rarely, 5= never

and then about hemophilia and the **SUPPORT YOU FELT YOU WERE RECEIVING**

	In the past month...	never	rarely	some-times	often	all the time
1.	... others showed special consideration for me because of my hemophilia	☐	☐	☐	☐	☐
2.	... others showed understanding for my hemophilia	☐	☐	☐	☐	☐
3.	... I was able to talk to others about problems with my hemophilia	☐	☐	☐	☐	☐
4.	... others stood by me	☐	☐	☐	☐	☐

These questions are about your hemophilia and **OTHER PEOPLE**

	In the past month...	never	rarely	some-times	often	all the time
1.	... I felt different from others because of my hemophilia	☐	☐	☐	☐	☐
2.	... I was bothered by others knowing about my hemophilia	☐	☐	☐	☐	☐
3.	... others kids teased me because of my hemophilia	☐	☐	☐	☐	☐
4.	... people behaved differently towards me because of my hemophilia	☐	☐	☐	☐	☐
5.	... I felt left out when others did things together	☐	☐	☐	☐	☐
6.	... others made dumb comments about my hemophilia	☐	☐	☐	☐	☐

Note: Questions 1 to 4 of the SUPPORT subscale are positively worded and are recoded so that numeric values assigned are reversed:

1=all the time, 2=often, 3=sometimes, 4=rarely, 5= never

These questions are about SPORTS AND SCHOOL						
	In the past month...	never	rarely	some-times	often	all the time
1.	... I had to avoid sports that I like because of my hemophilia	☐	☐	☐	☐	☐
2.	... I had to do indoor activities more than other kids because of my hemophilia	☐	☐	☐	☐	☐
3.	... I had to avoid sports like football or skateboarding	☐	☐	☐	☐	☐
4.	... I played sports just as much as any other kid	☐	☐	☐	☐	☐
5.	... I was treated differently by teachers because of my hemophilia	☐	☐	☐	☐	☐
6.	... I participated in gym class/PE at school even with my hemophilia	☐	☐	☐	☐	☐
7.	... I was able to participate at school even with my hemophilia	☐	☐	☐	☐	☐
8.	... I had to avoid special school events (e.g., field trips) because of my hemophilia	☐	☐	☐	☐	☐
9.	... I found it difficult to pay attention at school because I was in pain	☐	☐	☐	☐	☐

Note: Questions 4, 6 and 7 are positively worded and are recoded so that numeric values assigned are reversed:

1=all the time, 2=often, 3=sometimes, 4=rarely, 5= never

The next questions are about **DEALING WITH HEMOPHILIA**

	In the past month...	never	rarely	some-times	often	all the time
1.	… I tried to recognize early on when a bleed developed	☐	☐	☐	☐	☐
2.	... I was careful with my body	☐	☐	☐	☐	☐
3.	... I was able to tell whether or not I was bleeding	☐	☐	☐	☐	☐
4.	... I felt that my hemophilia symptoms were under control	☐	☐	☐	☐	☐
5.	... I felt well informed about hemophilia	☐	☐	☐	☐	☐
6.	... hemophilia was a normal part of my life	☐	☐	☐	☐	☐
7.	... I accepted having hemophilia	☐	☐	☐	☐	☐

Note: Questions 1 to 7 are positively worded and are recoded so that numeric values assigned are reversed:

1=all the time, 2=often, 3=sometimes, 4=rarely, 5= never

and what about your **TREATMENT**?

	In the past month...	never	rarely	some-times	often	all the time
1.	... I was satisfied with the hemophilia center	☐	☐	☐	☐	☐
2.	... the treatment I got was okay	☐	☐	☐	☐	☐
3.	... I trusted my doctors and nurses	☐	☐	☐	☐	☐
4.	... I disliked visiting the hemophilia center	☐	☐	☐	☐	☐
5.	... I felt dependent on others because of my hemophilia	☐	☐	☐	☐	☐
6.	... the injections annoyed me	☐	☐	☐	☐	☐
7.	... I was annoyed about the amount of time spent having the injections	☐	☐	☐	☐	☐
8.	... I felt the injections interrupted my activities	☐	☐	☐	☐	☐

What do you think about the **FUTURE**?

	Recently...	never	rarely	some-times	often	all the time
1.	... I have been thinking that it will be difficult for me to lead a normal life	☐	☐	☐	☐	☐
2.	... I have been expecting that things will get better as I grow older	☐	☐	☐	☐	☐
3.	... I have been worrying about my health	☐	☐	☐	☐	☐
4.	... I have been sure about having a family later on	☐	☐	☐	☐	☐

Note: Questions 1, 2 and 3 of the TREATMENT subscale and Questions 2 and 4 of the FUTURE subscale are positively worded and are recoded so that numeric values assigned are reversed:

1=all the time, 2=often, 3=sometimes, 4=rarely, 5= never

What about **RELATIONSHIPS**?

	Recently...	never	rarely	some-times	often	all the time
1.	... I have been finding it difficult to date because of my hemophilia	☐	☐	☐	☐	☐
2.	... I have been insecure in my relationships with girls because of my hemophilia	☐	☐	☐	☐	☐

And your **OVERALL HEALTH**?

	In general, ...	excellent	very good	good	fair	poor
1.	… would you say your health is…	☐	☐	☐	☐	☐

Open Questions

1. How much are you bothered by your hemophilia?

   ☐ not at all ☐ a little ☐ moderately ☐ considerably ☐ very much

2. What bothers you most about hemophilia? Please write down some things:

   - _____
   - _____
   - _____

3. What did you think of the questionnaire?

   (Please put a mark on the line between "0" and "100" to show what you think of the questionnaire.)

   0 100

   very poor very good

4. Have we forgotten anything that is important to you?

   - _____
   - _____
   - _____

5. How long did it take to fill out the questionnaire? About _____ minutes

Great job - congratulations!

THANK YOU FOR YOUR ASSISTANCE!

HAEM-A-QoL Adult Questionnaire

CIII-Haemo – QOL - USA/English – Final version – 29 June 07.

HAEM-A- QOL

Questionnaire for Adults

Dear Patient,

We would like to find out how you have been feeling during the past weeks. Please be so kind as to answer the following questions in this questionnaire, designed specifically for people with hemophilia.

Please follow the instructions below when answering the questions:

- ⇨ Please read each question carefully.
- ⇨ Think about how things have been for you over the past weeks.
- ⇨ Put an "X" in the box corresponding to the answer that fits you best.
- ⇨ Only mark one box for each question.
- ⇨ There are no right or wrong answers.
- ⇨ It's what you think that matters.
- ⇨ There are some aspects that might not concern you (Sports & Leisure, Family Planning, Work & School, e.g., if you don't work or don't go to school). In such a case, please mark the answer category "not applicable."

All your answers will be treated with the strictest confidence!

Date of completion: __ / __ / __ (month/ day/ year)

1. Here we would like to find out about hemophilia and your PHYSICAL HEALTH

	In the past month...	never	rarely	sometimes	often	all the time
1.	... my swellings hurt	☐	☐	☐	☐	☐
2.	... I had pain in my joints	☐	☐	☐	☐	☐
3.	... it was painful for me to move	☐	☐	☐	☐	☐
4.	... I had difficulty walking as far as I wanted to	☐	☐	☐	☐	☐
5.	… I needed more time to get ready because of my condition	☐	☐	☐	☐	☐

2. and now about how you have been FEELING because of your hemophilia

	In the past month...	never	rarely	sometimes	often	all the time
1.	... my hemophilia was a burden for me	☐	☐	☐	☐	☐
2.	... my hemophilia made me angry	☐	☐	☐	☐	☐
3.	... I was worried because of my hemophilia	☐	☐	☐	☐	☐
4.	... I felt excluded	☐	☐	☐	☐	☐

3. How does hemophilia affect your VIEW OF YOURSELF?

In the past month...	never	rarely	sometimes	often	all the time
1. ... I envied healthy people my age	☐	☐	☐	☐	☐
2. ... I felt comfortable with my body	☐	☐	☐	☐	☐
3. ... hemophilia made my life more difficult	☐	☐	☐	☐	☐
4. ... I felt different from others because of my hemophilia	☐	☐	☐	☐	☐
5. … I was able not to think all the time about my hemophilia	☐	☐	☐	☐	☐

4. These questions are about SPORTS AND LEISURE

In the past month...	never	rarely	some-times	often	all the time	not applicable
1. ... I had to avoid sports that I like because of my hemophilia	☐	☐	☐	☐	☐	☐
2. ... I had to avoid sports like football	☐	☐	☐	☐	☐	☐
3. … I played sports just as much as others	☐	☐	☐	☐	☐	☐
4. … I didn't have the freedom to travel where I wanted	☐	☐	☐	☐	☐	☐
5. … it was necessary for me to plan everything in advance	☐	☐	☐	☐	☐	☐

Note: Questions 2 and 5 of the VIEW OF YOURSELF subscale and Question 3 of the SPORTS AND LEISURE subscale are positively worded and are recoded so that numeric values assigned are reversed:

1=all the time, 2=often, 3=sometimes, 4=rarely, 5= never

5. These questions are about WORK AND SCHOOL

In the past month...	never	rarely	some-times	often	all the time	not applicable
1. ... I was able to go to work/school regularly in spite of my hemophilia	☐	☐	☐	☐	☐	☐
2. ... I was able to work/study like healthy colleagues	☐	☐	☐	☐	☐	☐
3. ... my everyday work/school activities were jeopardized by my hemophilia	☐	☐	☐	☐	☐	☐
4. ... I found it difficult to pay attention at work/school because I was in pain	☐	☐	☐	☐	☐	☐

6. The next questions are about DEALING WITH HEMOPHILIA

In the past month...	never	rarely	sometimes	often	all the time
1. ... I tried to recognize early on when a bleed developed	☐	☐	☐	☐	☐
2. ... I was able to tell whether or not I was bleeding	☐	☐	☐	☐	☐
3. ... I was able to control my bleeds	☐	☐	☐	☐	☐

Note: Questions 1 and 2 of the WORK AND SCHOOL subscale and Questions 1 to 3 of the DEALING WITH HEMOPHILIA subscale are positively worded and are recoded so that numeric values assigned are reversed:

1=all the time, 2=often, 3=sometimes, 4=rarely, 5= never

7. and what about your TREATMENT?

In the past month...	never	rarely	sometimes	often	all the time
1. … I was dependent on the factor concentrate because of my hemophilia	☐	☐	☐	☐	☐
2. … I was dependent on physicians for the treatment of my hemophilia	☐	☐	☐	☐	☐
3. ... I was annoyed about the amount of time spent having the injections	☐	☐	☐	☐	☐
4. ... I felt the injections interrupted my daily activities	☐	☐	☐	☐	☐
5. … I was afraid of complications	☐	☐	☐	☐	☐
6. … I had problems with how my treatment was administered	☐	☐	☐	☐	☐
7. … I was afraid that in case of emergency, other doctors wouldn't know how to treat hemophilia	☐	☐	☐	☐	☐
8. … I was satisfied with the hemophilia center	☐	☐	☐	☐	☐

Note: Question 8 is positively worded and is recoded so that numeric values assigned are reversed:

1=all the time, 2=often, 3=sometimes, 4=rarely, 5= never

8. What do you think about the FUTURE?

Recently...	never	rarely	sometimes	often	all the time
1. ... I have been thinking that it will be difficult for me to lead a normal life	☐	☐	☐	☐	☐
2. ... I have been expecting that things will get better in the future	☐	☐	☐	☐	☐
3. ... I have been worrying that my condition is worsening	☐	☐	☐	☐	☐
4. ... my life plans have been influenced by my hemophilia	☐	☐	☐	☐	☐
5. ... I have been afraid that I will need a wheelchair	☐	☐	☐	☐	☐

9. The next questions are about hemophilia and your FAMILY PLANNING

Recently...	never	rarely	some-times	often	all of the time	not applicable
1. ... I have had difficulties having children	☐	☐	☐	☐	☐	☐
2. ... I have been afraid that I cannot have children	☐	☐	☐	☐	☐	☐
3. ... I have been afraid that I will not be able to take care of my children	☐	☐	☐	☐	☐	☐
4. ... I have been worrying about not being able to raise a family	☐	☐	☐	☐	☐	☐

Note: Question 2 of the FUTURE subscale is positively worded and is recoded so that numeric values assigned are reversed:

1=all the time, 2=often, 3=sometimes, 4=rarely, 5= never

10. What about PARTNERSHIP AND SEXUALITY?

	Recently...	never	rarely	sometimes	often	all the time
1.	... I have been finding it difficult to date because of my hemophilia	☐	☐	☐	☐	☐
2	... I have been insecure in my relationships with women because of my hemophilia	☐	☐	☐	☐	☐
3.	… I haven't been able to have a normal relationship because of my hemophilia	☐	☐	☐	☐	☐

THANK YOU FOR YOUR ASSISTANCE!

APPENDIX D. EQ-5D-3L QUESTIONNAIRE SCORE DEFINITIONS

Domain	Response	Score
Mobility	I have no problems in walking about	1
	I have some problems in walking about	2
	I am confined to bed	3
Self-care	I have no problems with self-care	1
	I have some problems washing or dressing myself	2
	I am unable to wash or dress myself	3
Usual activities	I have no problems with performing my usual activities	1
	I have no problems with performing my usual activities	2
	I am unable to perform my usual activities	3
Pain/discomfort	I have no pain or discomfort	1
	I have moderate pain or discomfort	2
	I have extreme pain or discomfort	3
Anxiety/depression	I am not anxious or depressed	1
	I am moderately anxious or depressed	2
	I am extremely anxious or depressed	3

APPENDIX E. CHO-KLAT SCORING ALGORITHM AND QUESTIONNAIRES

1. Scoring

The items presented in the CHO-KLAT questionnaire are worded in both positive and negative directions whereas the responses to the questions are consistently scored as 1=Never, 2=Rarely, 3=Sometimes, 4=Often, and 5=Always. Therefore, the negatively-worded questions need to be rescored as 5=Never, 4=Rarely, 3=Sometimes, 2=Often, and 1=Always so that a high score represent a high quality of life. After the rescoring the unidirectional values can be added to yield a total score.

Positively worded questions include numbers 1, 2, 7, 12 through 14, 19 through 22, 29, 30, and 35.

Negatively worded questions include numbers 3 through 6, 8 through 11, 15 through 18, 23 through 28, and 31 through 34.

Questions 23 through 35 include an additional response that indicates that the question is not applicable to the respondent. A response indicating that the situation is not applicable to the subject for questions 23, 24, 26 through 29, and 34 should receive a score of 5. A response indicating that the situation is not applicable to the subject for questions 22, 25, 30 through 33, and 35 should be scored as missing data as these situations have neither a positive nor negative impact on quality of life.

2. Producing the raw total score

The raw total score is produced by summing up all of items that were answered. Its range lies between the number of items answered × 1 and the number of items answered × 5. The highest possible score is 175. Applying a minimum data rule of 75%, at least 27 questions must be answered in order to obtain a total score.

3. Transferring the raw total score to a Transformed Score between 0 and 100

Creating a transformed score makes it possible to express the score as a percentage between the lowest (0) and the highest (100) possible value. To obtain the transformed score the following transformation rule has to be applied:

Transformed score= 100 × ((raw score – minimal possible raw score) / possible range of raw scores) where:

- minimal possible raw score = number of questions answered × 1
- maximal possible raw score = number of questions answered × 5
- possible range of raw scores = maximum possible raw score - minimal possible raw score

Example 1: A raw total score of 60 is to be transformed when 30 questions were answered:

- minimal possible score=30
- maximal possible score=150
- range of scores=120
- TSS=100× (60-30)/120 = 25.0

Example 2: A raw total score of 110 is to be transformed when 28 questions were answered:

- minimal possible score=28
- maximal possible score=140
- range of scores=112
- TSS=100× (110-28)/112 = 73.2

The total transformed score will be summarized.

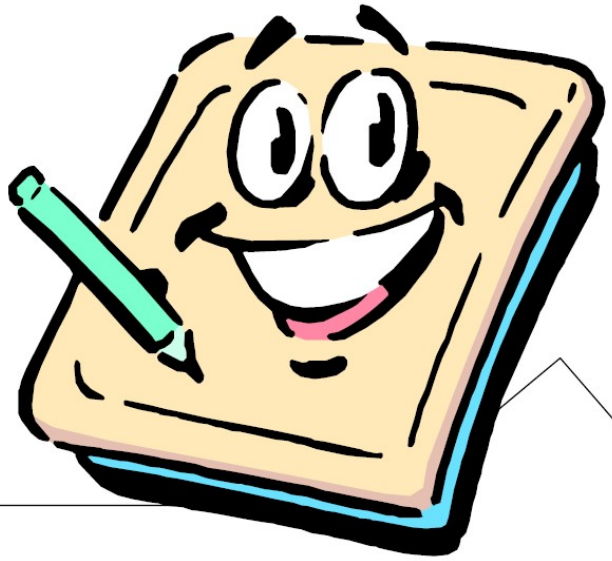
A copy of the questionnaire is provided below. Items are highlighted when they require re-coding as detailed in point 1 above.

CHO-KLAT Child Self-report Questionnaire

United States English CHO-KLAT 2.0 – Child Self-Report February 23-12

CHO-KLAT

Canadian Hemophilia Outcomes
– Kids' Life Assessment Tool
Version 2.0



Hello…
My friends and I would like to know how you have been feeling, so we came up with a few questions for you to answer.

Remember: choose the best answer for you (**one answer only** for each question)

For Example:

In the past 4 weeks …	Never	Hardly ever	Sometimes	Often	Always
1. I wanted to go bike riding	○	☑	○	○	○

Some of the questions have another answer to pick if these things did not happen to you.

For Example:

In the past 4 weeks …	Never	Hardly ever	Sometimes	Often	Always
2. I wrote a story at school	○	○	○	○	○

or ☑ I did not go to school in the past 4 weeks.

Please tell us how often these things happened to you.

In the past 4 weeks…	Never	Hardly ever	Some-times	Often	Always
1. I felt as healthy as other kids my age	❍	❍	❍	❍	❍
2. I was happy about my body	❍	❍	❍	❍	❍
3. It bothered me that I couldn't play the sports that I like	❍	❍	❍	❍	❍
4. It bothered me that my parents wouldn't let me do some things	❍	❍	❍	❍	❍
5. I kept (hid) things about my hemophilia from my parents	❍	❍	❍	❍	❍
6. I worried about my health	❍	❍	❍	❍	❍
7. I was happy even though I have hemophilia	❍	❍	❍	❍	❍
8. I made an effort to forget that I have hemophilia	❍	❍	❍	❍	❍
9. I worried that if I were hurt my body wouldn't be the same again	❍	❍	❍	❍	❍
10. I got upset that some health care professionals (doctors or nurses) didn't really understand hemophilia	❍	❍	❍	❍	❍
11. I was very afraid of a serious joint bleed	❍	❍	❍	❍	❍
12. I liked playing outside with my friends	❍	❍	❍	❍	❍
13. I was able to talk to my friends about my hemophilia	❍	❍	❍	❍	❍
14. I was able to talk to others about my hemophilia	❍	❍	❍	❍	❍
15. It bothered me that I missed special school events	❍	❍	❍	❍	❍
16. I felt overprotected by others	❍	❍	❍	❍	❍

In the past 4 weeks…	Never	Hardly ever	Some-times	Often	Always
17. My parents nagged (bothered) me about wearing the right protective equipment (like helmets)	❍	❍	❍	❍	❍
18. I needed to know more about hemophilia	❍	❍	❍	❍	❍
19. I felt like I had some control of my life	❍	❍	❍	❍	❍
20. I knew what to do if I got hurt	❍	❍	❍	❍	❍
21. I liked it when I was included in decisions about my care	❍	❍	❍	❍	❍

The next group of questions <u>have another answer to pick</u> if these things did not happen to you.

In the past 4 weeks…	Never	Hardly ever	Some-times	Often	Always
22. The treatment I got was okay	❍	❍	❍	❍	❍
or ❑ I did not get treatment in the past 4 weeks.					
23. I had to stay still when I had a bleed	❍	❍	❍	❍	❍
or ❑ I did not have any bleeds in the past 4 weeks.					
24. I put off (avoided) treatment	❍	❍	❍	❍	❍
or ❑ I did not need treatment in the past 4 weeks.					
25. Factor infusions bothered me	❍	❍	❍	❍	❍
or ❑ I did not have factor infusions in the past 4 weeks.					

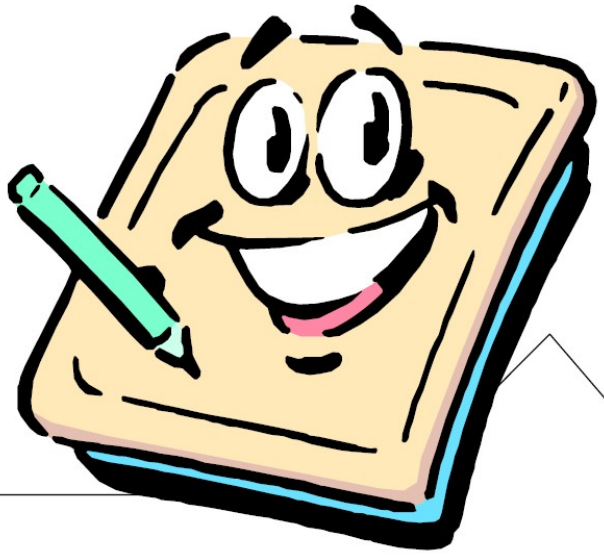
In the past 4 weeks…	Never	Hardly ever	Some-times	Often	Always
26. Other treatments (like icing, rest, physical therapy) were annoying	❍	❍	❍	❍	❍
or ❑ I did not have other treatments in the past 4 weeks.					
27. I got upset about my limits in physical activity	❍	❍	❍	❍	❍
or ❑ I was not limited in physical activities in the past 4 weeks.					
28. I hid my pain	❍	❍	❍	❍	❍
or ❑ I did not have any pain in the past 4 weeks.					
29. I told my parents right away about my bleeds	❍	❍	❍	❍	❍
or ❑ I did not have bleeds in the past 4 weeks.					
30. Home infusions made my life easier	❍	❍	❍	❍	❍
or ❑ I did not have home infusions in the past 4 weeks.					
31. It bothered me that I had to take factor with me when I traveled	❍	❍	❍	❍	❍
or ❑ I did not travel in the past 4 weeks.					
32. It bothered me when strangers were nosy about my hemophilia	❍	❍	❍	❍	❍
or ❑ Strangers were not nosy about my hemophilia in the past 4 weeks.					
33. I was upset because sports were getting harder for me to play	❍	❍	❍	❍	❍
or ❑ Sports did not get harder to play in the past 4 weeks.					
34. Having a bleed away from home was scary	❍	❍	❍	❍	❍
or ❑ I did not have a bleed away from home in the past 4 weeks.					
35. Self-infusions let me have more freedom	❍	❍	❍	❍	❍
or ❑ I did not self-infuse in the past 4 weeks.					

CHO-KLAT Parent/Proxy Questionnaire

United States English CHO-KLAT 2.0 – Parent/Proxy Report February 23-12

CHO-KLAT

Canadian Hemophilia Outcomes
– Kids' Life Assessment Tool
Version 2.0



Dear Parent/Guardian,

Thank you for taking the time to complete this questionnaire about your son's well-being and health-related quality of life. Please complete the questionnaire without sharing any answers with your son.

Instructions:

- Only one parent/guardian should answer the questions.
- Are you the:

  ☐ Mother ☐ Father ☐ Other _____

- Please think about how your son has been feeling during the past 4 weeks and answer the questions as they apply to your son.

Please tell us how often these things happened to your son.

In the past 4 weeks…	Never	Hardly ever	Some-times	Often	Always
1. My son felt as healthy as other kids his age	❍	❍	❍	❍	❍
2. My son was happy about his body	❍	❍	❍	❍	❍
3. It bothered my son that he couldn't play the sports that he likes	❍	❍	❍	❍	❍
4. It bothered my son that our family wouldn't let him do some things	❍	❍	❍	❍	❍
5. My son kept (hid) things from me about his hemophilia	❍	❍	❍	❍	❍
6. My son worried about his health	❍	❍	❍	❍	❍
7. My son was happy even though he has hemophilia	❍	❍	❍	❍	❍
8. My son made an effort to forget that he has hemophilia	❍	❍	❍	❍	❍
9. My son worried that if he were hurt his body wouldn't be the same again	❍	❍	❍	❍	❍
10. My son got upset that some health care professionals (doctors or nurses) didn't really understand hemophilia	❍	❍	❍	❍	❍
11. My son was very afraid of a serious joint bleed	❍	❍	❍	❍	❍
12. My son liked playing outside with his friends	❍	❍	❍	❍	❍
13. My son was able to talk to his friends about his hemophilia	❍	❍	❍	❍	❍
14. My son was able to talk to others about his hemophilia	❍	❍	❍	❍	❍
15. It bothered my son that he missed special school events	❍	❍	❍	❍	❍
16. My son felt overprotected by others	❍	❍	❍	❍	❍

In the past 4 weeks…	Never	Hardly ever	Some-times	Often	Always
17. Our family nagged (bothered) my son about wearing the right protective equipment (like helmets)	❍	❍	❍	❍	❍
18. My son needed to know more about hemophilia	❍	❍	❍	❍	❍
19. My son felt like he had some control of his life	❍	❍	❍	❍	❍
20. My son knew what to do if he got hurt	❍	❍	❍	❍	❍
21. My son liked when he was included in decisions about his care	❍	❍	❍	❍	❍

The next group of questions <u>have another answer to pick</u> if these things did not happen to your son.

In the past 4 weeks…	Never	Hardly ever	Some-times	Often	Always
22. The treatment my son got was okay **or** ❑ My son did not get treatment in the past 4 weeks.	❍	❍	❍	❍	❍
23. My son had to stay still when he had a bleed **or** ❑ My son did not have any bleeds in the past 4 weeks.	❍	❍	❍	❍	❍
24. My son put off (avoided) treatment **or** ❑ My son did not need treatment in the past 4 weeks.	❍	❍	❍	❍	❍
25. Factor infusions bothered my son **or** ❑ My son did not have factor infusions in the past 4 weeks.	❍	❍	❍	❍	❍
26. Other treatments (like icing, rest, physical therapy) were annoying for my son **or** ❑ My son did not have other treatments in the past 4 weeks.	❍	❍	❍	❍	❍

In the past 4 weeks…	Never	Hardly ever	Some-times	Often	Always
27. My son got upset about his limits in physical activity	❍	❍	❍	❍	❍
or ❑ My son was not limited in physical activities in the past 4 weeks.					
28. My son hid his pain	❍	❍	❍	❍	❍
or ❑ My son did not have any pain in the past 4 weeks.					
29. My son told me right away about his bleeds	❍	❍	❍	❍	❍
or ❑ My son did not have bleeds in the past 4 weeks.					
30. Home infusions made my son's life easier	❍	❍	❍	❍	❍
or ❑ My son did not have home infusions in the past 4 weeks.					
31. It bothered my son to take factor with him when he traveled	❍	❍	❍	❍	❍
or ❑ My son did not travel in the past 4 weeks.					
32. It bothered my son when strangers were nosy about his hemophilia	❍	❍	❍	❍	❍
or ❑ Strangers were not nosy about my son's hemophilia in the past 4 weeks.					
33. My son was upset because sports were getting harder for him to play	❍	❍	❍	❍	❍
or ❑ Sports did not get harder for my son to play in the past 4 weeks.					
34. Having a bleed away from home was scary for my son	❍	❍	❍	❍	❍
or ❑ My son did not have a bleed away from home in the past 4 weeks.					
35. Self-infusions let my son have more freedom	❍	❍	❍	❍	❍
or ❑ My son did not self-infuse in the past 4 weeks.					

APPENDIX F. HEMO-SAT SCORING ALGORITHM AND QUESTIONNAIRE

The Hemo-Sat Patient Satisfaction scale is a 35-item questionnaire encompassing 6 subscales regarding the subject's and parent/caregiver's satisfaction with various aspects of the treatment and care the subject.

1. Scoring

The items presented in the Hemo-Sat questionnaire are worded in both positive and negative directions whereas the responses to the questions are consistently scored as 1=Totally agree, 2=Somewhat agree, 3=Neither agree nor disagree, 4=Somewhat disagree, and 5=Totally disagree. Therefore, the negatively-worded questions need to be rescored as 5=Totally agree, 4=Somewhat agree, 3=Neither agree nor disagree, 2=Somewhat disagree, and 1=Totally disagree so that a high score represent a high satisfaction with the treatment. After the rescoring the unidirectional values can be added to yield 6 subscores and a total score.

Negatively worded questions include numbers 9 through 11. The 32 remaining questions are all positively worded.

2. Producing the raw total and subscale scores

The raw total score is produced by summing up all of items that were answered across all 35 questions. Its range lies between the number of items answered × 1 and the number of items answered × 5. The highest possible score is 175. Applying a minimum data rule of 75%, at least 27 questions must be answered in order to obtain a total score.

Similarly, a raw subscale score is produced by summing up all items that were answered within a subscale. The range of values lies between the number of items that were answered × 1 and the number of items that were answered × 5 in a given subscale. The minimum number of questions answered for each subscale, applying a minimum data rule of 75%, is as follows:

Hemo-Sat Subscale	Number of questions	Number of non-missing items required to calculate subscale
1. Ease and convenience	11	9
2. Efficacy	6	5
3. Burden	4	3
4. Specialist/Nurses	7	6
5. Center/Hospital	5	4
6. General satisfaction with the treatment	2	2
Total score	35	27

3. Transferring a raw score to a Standardized (average) score

The Standardized score is the average of all items with a nonmissing score. That is, missing items do not contribute to either the numerator or denominator. This effectively imputes the

mean of all nonmissing items for the items that are missing, allowing for a comparison between subscales.

4. Transferring a raw score to a Transformed Score between 0 and 100

Creating a transformed score makes it possible to express the score as a percentage between the lowest (0) and the highest (100) possible value. To obtain the transformed score the following transformation rule has to be applied:

Transformed score= 100 × ((raw score – minimal possible raw score) / possible range of raw scores) where:

- minimal possible raw score = number of questions answered × 1
- maximal possible raw score = number of questions answered × 5
- possible range of raw scores = maximum possible raw score - minimal possible raw score

Example 1: A raw score of 17 on the "Center/Hospital" subscale is to be transformed when all 5 of the questions were answered:

- minimal possible score=5
- maximal possible score=25
- range of scores=20
- TSS=100×(17-5)/20 = 60.0

Example 2: A raw score of 20 on the "Specialist/Nurse" subscale is to be transformed when 6 of the 7 questions were answered:

- minimal possible score=6
- maximal possible score=30
- range of scores=24
- TSS=100×(20-6)/24 = 58.3

The total and subscale transformed score will be summarized.

A copy of the questionnaire is provided below. Items are highlighted when they require re-coding as detailed in point 1 above.

HEMO-SAT QUESTIONNAIRE

Hemo-Sat$_P$ - Hemophilia treatment satisfaction questionnaire (ENGLISH FOR THE USA version parents) 15.05.09

Hemo-Sat
Patient Satisfaction Scale

Hello there!

We would like to know how satisfied you are with your son's hemophilia treatment. We have a few questions that we would like you to answer. This questionnaire was made for parents of children with hemophilia.

- ⇨ Please read each question carefully.
- ⇨ Choose the answer that fits you best and check the appropriate box.
- ⇨ There are no right or wrong answers.
- ⇨ It's what you think that matters.

For example:	totally agree	somewhat agree	neither agree nor disagree	somewhat disagree	totally disagree
I'm satisfied with my son's life in general	☐	☒	☐	☐	☐

Date of completion: __ / __ / __ (month / day / year)

We would like to know how satisfied you are with the following aspects concerning YOUR SON'S HEMOPHILIA TREATMENT?

1. Ease and convenience

How much do you agree with the following statements?	totally agree	somewhat agree	neither agree nor disagree	somewhatd isagree	totally disagree
1. Treatment does not interfere with our everyday life	☐	☐	☐	☐	☐
2. I am satisfied with the number of doctor's appointments associated with my son's treatment	☐	☐	☐	☐	☐
3. It is easy to prepare the infusion	☐	☐	☐	☐	☐
4. I am satisfied with the volume of the infusion	☐	☐	☐	☐	☐
5. I am satisfied with the way that the medication is administered	☐	☐	☐	☐	☐
6. I am satisfied with the way that I have to store the medication	☐	☐	☐	☐	☐
7. I am satisfied with how often my son must be infused	☐	☐	☐	☐	☐
8. I feel that his medication is safe	☐	☐	☐	☐	☐
9. I worry about the risk of inhibitors associated with his medication	☐	☐	☐	☐	☐
10. I am bothered by side effects caused by his medication	☐	☐	☐	☐	☐
11. I worry about the risk of infection associated with his medication	☐	☐	☐	☐	☐

2. Efficacy

How much do you agree with the following statements?	totally agree	somewhat agree	neither agree nor disagree	somewhat disagree	totally disagree
1. I am satisfied with the time needed for the medication to stop my son's bleed	☐	☐	☐	☐	☐
2. I am satisfied with the number of injections that are normally needed to stop a bleed	☐	☐	☐	☐	☐
3. I am confident that, if he takes the medication in advance, he can prevent a bleed	☐	☐	☐	☐	☐
4. I am satisfied with the ability of the medication to control my son's bleeds	☐	☐	☐	☐	☐
5. I am confident that he can have a normal life when he follows the prescribed treatment	☐	☐	☐	☐	☐
6. I am satisfied with the activities he is allowed to do with his treatment	☐	☐	☐	☐	☐

3. Burden

How much do you agree with the following statements?	totally agree	somewhat agree	neither agree nor disagree	somewhat disagree	totally disagree
1. The medication does not cause my son any discomfort	☐	☐	☐	☐	☐
2. My son doesn't worry about receiving his medication	☐	☐	☐	☐	☐
3. I have full confidence in his medication	☐	☐	☐	☐	☐
4. I am pleased to be able to control his disease myself	☐	☐	☐	☐	☐

4. Specialist/Nurses

How much do you agree with the following statements?	totally agree	somewhat agree	neither agree nor disagree	somewhat disagree	totally disagree
1. I am satisfied with the information that I received about my son's medication from his doctor	☐	☐	☐	☐	☐
2. I am satisfied with the information I received about his options for treatment	☐	☐	☐	☐	☐
3. I am satisfied with the quality of care that he receives	☐	☐	☐	☐	☐
4. I have confidence in the doctor's recommendations for my son's hemophilia treatment	☐	☐	☐	☐	☐
5. I am satisfied with the doctor's explanation of my son's health condition	☐	☐	☐	☐	☐
6. I am satisfied with the time my son's doctor spends with us	☐	☐	☐	☐	☐
7. I feel the doctor understands us and our problems	☐	☐	☐	☐	☐

5. Center/Hospital

How much do you agree with the following statements?	totally agree	somewhat agree	neither agree nor disagree	somewhat disagree	totally disagree
1. I am satisfied with the availability of the person on duty at the center/hospital	☐	☐	☐	☐	☐
2. We feel comfortable at the center/hospital	☐	☐	☐	☐	☐
3. I am satisfied with our relationship with his doctor	☐	☐	☐	☐	☐
4. I am satisfied with our relationships with the nurses	☐	☐	☐	☐	☐
5. I am confident that his center takes good care of him	☐	☐	☐	☐	☐

6. GENERAL SATISFACTION with the treatment

How much do you agree with the following statements?	totally agree	rather agree	neither agree nor disagree	somewhat disagree	totally disagree
1. I am generally satisfied with his treatment	☐	☐	☐	☐	☐
2. I am satisfied with his medication	☐	☐	☐	☐	☐

THANK YOU FOR YOUR ASSISTANCE!

APPENDIX G. EQ-5D-Y QUESTIONNAIRE SCORE DEFINITIONS

Domain	Response
Mobility	I have no problems walking about I have some problems walking about I have a lot of problems walking about
Looking after myself	I have no problems washing or dressing myself I have some problems washing or dressing myself I have a lot of problems washing or dressing myself
Doing usual activities	I have no problems doing my usual activities I have some problems doing my usual activities I have a lot of problems doing my usual activities
Having pain/discomfort	I have no pain or discomfort I have some pain or discomfort I have a lot of pain or discomfort
Feeling worried, sad or unhappy	I am not worried, sad, or unhappy I am a bit worried, sad, or unhappy I am very worried, sad, or unhappy
How good is your health today	

APPENDIX H. HEMOPHILIA JOINT HEALTH SCORE (HJHS)

Modified HJJS for adult subjects

Six joints (left ankle-LA, right ankle-RA, left elbow-LE, right elbow-RE, left knee-LK, right knee-RK) will be scored on a scale from 0 to 19 according to the following criteria: swelling, duration, muscle atrophy, crepitus, flexion loss, extension loss, instability, joint pain, and strength. Gait will be scored on a scale from 0 to 2 based on walking and climbing stairs. The total score will be the sum of scores from all 6 joints plus the gait score (range from 0 to 116 with, 0 being normal and 116 being the most severe disease).

SCORING DETAILS

1. **Joint scoring will be done separately for the 6 joints (LA, RA, LE, RE, LK, RK) according to these categories and scales (range is 0-19 for each joint and 0-114 for all six joints):**

   Swelling

   0=none

   1=mild

   2=moderate

   3= severe

   Duration of swellling

   0=no swelling or < 6 months

   1= >6 months

   Muscle atrophy

   0=none

   1=mild

   2=severe

   Crepitus on motion

   0=absent

   1=present

   Flexion loss (includes plantarflexion of ankles)

   0=none*

   1= mild*

   2= moderate*

   3= severe*

   Extension loss (includes dorsiflexion of ankles)

0= none*

1= mild*

2= moderate*

3= severe*

* Use the following as guidance for scoring flexion loss and extension loss at knees and elbows:

None: approximately 0-5 degrees

Mild: approximately 5-10 degrees

Moderate: approximately 11-20 degrees

Severe: approximately >20 degrees

Instability

0=none

1=significant pathologic joint laxity

Joint pain

0=no pain (either through range or at end range of motion)

1=present

Strength

0=normal (holds position against gravity and maximum resistance)

1=minimal decrease (holds position against gravity and moderate resistance, but not maximum resistance)

2=mild decrease (holds position against gravity or minimal resistance)

3=moderate decrease (able to move joint if gravity eliminated)

4=severe decrease (trace or no muscle contraction)

2. Gait will be scored once (range is 0-2):

0=No difficulty with walking or climbing up/down stairs

1=No difficulty with walking, but difficulty with stairs

2=Difficulty with walking and with stairs

Total score = sum of all joint scores plus the gait score (range is 0-116)

HJHS for pediatric subjects

Six joints (left ankle-LA, right ankle-RA, left elbow-LE, right elbow-RE, left knee-LK, right knee-RK) will be scored on a scale from 0 to 20 according to the following criteria: swelling, duration of swelling, muscle atrophy, crepitus of motion, flexion loss, extension loss, joint pain, and strength. Gait will be scored on a scale from 0 to 4 based on the number of skills not within the normal limits. The total score will be the sum of scores from all 6 joints plus the gait score (range from 0 to 124 with 0 being normal and 124 being the most severe disease).

SCORING DETAILS

1. Joint scoring will be done separately for the 6 joints (LA, RA, LE, RE, LK, RK) according to these categories and scales (range is 0-20 for each joint and 0-120 for all six joints):

Swelling

0 = no swelling

1 = mild

2 = moderate

3 = severe

Duration of swelling

0 = no swelling or <6 months

1 = ≥6 months

Muscle atrophy

0 = none

1 = mild

2 = severe

Crepitus on motion

0 = none

1 = mild

2 = severe

Flexion loss

0 = <5°

1 = 5° - 10°

2 = 11° - 20°

3 = >20°

Extension loss

0 = <5°

1 = 5° - 10°

2 = 11° - 20°

3 = >20°

Joint pain

0 = no pain through active range of motion

1 = no pain through active range; only pain on gentle overpressure or palpation

2 = pain through active range

Strength

0 = holds test position against gravity with maximum resistance (gr. 5)

1 = holds test position against gravity with moderate resistance (but breaks with maximal resistance (gr. 4)

2 = holds test position with minimal resistance (gr. 3+), or holds test position against gravity (gr. 3)

3 = able to partially complete ROM against gravity (gr. 3-/2+), or able to move through ROM gravity eliminated (gr. 2), or thorough partial ROM gravity eliminated (gr. 2-)

4 = trace (gr. 1) or no muscle contraction (gr. 0)

NE = non-evaluable

2. Gait will be scored once (range is 0-4):

0 = all skills are within normal limits

1 = One skill is not within normal limits

2 = Two skills are not within normal limits

3 = Three skills are not within normal limits

4 = No skills are within normal limits

NE = non-evaluable

Total score = sum of all joint scores plus the gait score (range is 0-124)