STATISTICAL ANALYSIS PLAN

BAX 855

Phase 3, prospective, randomized, multi-center clinical study comparing the safety and efficacy of BAX 855 following PK-guided prophylaxis targeting two different FVIII trough levels in subjects with severe Haemophilia A

PROTOCOL IDENTIFIER: 261303

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1. INTRODUCTION AND OBJECTIVES

This document describes the rules and conventions to use in the planned presentation and analysis of efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) data for Protocol 261303 as set out in the latest version of the Output Templates. It describes the data for summarizing and analyzing, including specifics of the statistical analyses that will be performed.

The purpose of this study is to compare the efficacy and safety of PK-guided treatment with BAX 855 targeting factor eight (FVIII) trough levels of 1-3% and approximately 10% (8-12%), and to further characterize PK and PD parameters of BAX 855 for prophylaxis and treatment of bleeding episodes in adult and adolescent subjects with severe haemophilia A, aged ≥12 years up to ≤65 years.

1.1 Study Objectives

1.1.1 Primary Objective

The primary objective of the study is to compare two prophylactic dosing regimens of BAX 855 targeting two different FVIII trough levels, by comparing the proportions of subjects achieving a total annualized bleeding rate (ABR) of 0 in the second 6-month study period.

1.1.2 Secondary Objectives

1.1.2.1 Efficacy

1. To compare the two treatment arms of BAX 855 targeting two different FVIII trough levels with respect to the following:

    - The proportion of subjects in each treatment arm achieving a spontaneous ABR and spontaneous joint bleeding rate (AJBR) of 0 in the second 6-month study period.
    - The proportion of subjects in each treatment arm with a total ABR, spontaneous ABR and AJBR <2.
    - The total ABR, spontaneous ABR, and trauma-related ABRs in the full 12-month study period.
    - The reduction in ABR between the two treatment arms and the historical ABR prior to study enrollment.
    - The total weight-adjusted consumption of BAX 855 for each treatment arm.
    - The joint status using the Haemophilia Joint Health Score (HJHS) over time.

- The Health-related Quality of life (HRQoL) and pharmacoeconomic outcomes as assessed by the following:
  a. Short form-36 questionnaire (SF-36).
  b. EuroQol-5 dimension (EQ-5D) questionnaire.
  c. Haemophilia-symptom (Haemo-SYM) questionnaire.
  d. Healthcare resource utilization (as recorded in the subject diaries).

2. To determine the hemostatic efficacy of BAX 855 in the control of bleeding episodes.

3. To evaluate the efficacy of BAX 855 for perioperative management, if surgery is required.

1.1.2.2 Safety

1. To determine the immunogenicity of BAX 855.
2. To determine the safety of BAX 855, as assessed by the following:
   - Occurrence of adverse events (AEs).
   - Changes in vital signs.
   - Changes in laboratory parameters.

1.1.2.3 Pharmacokinetics

1. To determine the PK parameters of BAX 855 at baseline and steady state, if applicable, and the correlation with pre-infusion von Willebrand Factor (VWF) antigen level.
2. To determine the incremental recovery (IR) over time.

1.1.2.4 Patient Reported Outcomes

1. To assess the difference in the SF-36 physical domain and component change scores from baseline to completion between subjects in the 1-3% trough arm (low level treatment arm) and subjects in the 10% trough arm (high level treatment arm).
2. To assess the difference in the change of days of physical activity participation from baseline to completion between subjects in the low level treatment arm and subjects in the high level treatment arm.

1.1.3 Exploratory Objectives

1. To determine the potential correlation between ABR and the FVIII trough levels as well as the correlation between ABR and the following thrombin generation assay (TGA) parameters:
    a. Lag time.
    b. Time to peak thrombin generation.
    c. Peak thrombin generation.
    d. Endogenous thrombin potential (ETP).
2. To assess the change in bleed and pain severity scores as measured by the Haemo-SYM questionnaire.
3. To assess the change in HRQoL using:
    a. The EQ-5D questionnaire.
    b. The mental domain and component scores of the SF-36 questionnaire.
4. To assess the difference in the change in healthcare resource utilization from baseline to completion between subjects in the 1-3% trough (low level treatment) arm and subjects in the 10% trough (high level treatment) arm.

2. STUDY DESIGN

This study is a Phase 3, prospective, randomized, open-label, multicenter study to compare the safety and efficacy of a PK-guided BAX 855 treatment regimen targeting two different FVIII trough levels of 1-3% and approximately 10% (8-12%) in adolescent and adult, previously treated patients (PTPs) with severe haemophilia A (<1% FVIII) between the ages of 12 and 65 years inclusive. The study plans to include subjects from other BAX 855 studies as well as BAX 855-naïve subjects.

Enrolled subjects are to undergo an initial PK assessment following a single administration of BAX 855 to determine the subject's individual PK parameters to tailor the dose for the targeted FVIII trough levels.

The duration of subject participation in the study is approximately 15 to 16 months from enrollment to subject completion (i.e. last study visit), unless prematurely discontinued.

An optional repeat PK assessment at steady state should be performed after nine months of treatment administration.

The use of any FVIII concentrate other than BAX 855 during the course of the study, following the first BAX 855 PK-guided prophylactic infusion at baseline, is not permitted and will result in the immediate withdrawal of the subject.

2.1 Inclusion Criteria

See Section 9.1: Inclusion Criteria, of the Clinical Study Protocol for information on inclusion criteria.

2.2 Exclusion Criteria

See Section 9.2: Exclusion Criteria, of the Clinical Study Protocol for information on exclusion criteria.

2.3 Sample Size and Power Calculations

For the sample size assessment the following assumptions were used. Approximately 40% of subjects in BAX 855 regimen targeting 1-3% trough level are expected to be bleed-free as shown in the ADVATE Prophylaxis study and the BAX 855 pivotal study 261201. For the BAX 855 regimen targeting approximately 10% (8-12%) trough level, an increase to 70% bleed-free subjects is expected based on modeling the bleeding rates per FVIII level in the BAX 855 pivotal study 261201.

Under these assumptions 48 subjects per study arm are needed to reject the null hypothesis of no difference between the study arms against a two-sided alternative at the 5% level of statistical significance with 80% power. Assuming a drop-out rate of close to 10%, and 10-15% of subjects being non-compliant, approximately 116 subjects are planned to be randomized between the two BAX 855 regimens with an allocation ratio of 1:1.

2.4 Randomization and Blinding

This is a randomized, open-label, concurrent, dose regimen comparison clinical study. In order to minimize/avoid bias, once eligibility is confirmed, subjects are randomly assigned to one of two treatment regimens with PK-guided dosing targeting FVIII trough levels of 1-3% or approximately 10% (8-12%) in a 1:1 ratio. Randomization occurs after the PK assessment and is stratified according to subjects' pre-study treatment regimen/ABR (prophylaxis with ABR <5 vs. prophylaxis with ABR ≥5 vs. on-demand).

2.5 Study Stopping Rules

This study will be halted (enrollment and treatment temporarily stopped), pending further review by the Sponsor, or stopped if one of the following criterion is met:

- Two or more subjects develop a high responder inhibitory antibody >5 Bethesda units (BU), confirmed by two measurements within a 2 to 4 week period at the central laboratory, after BAX 855 administration.
- Two or more subjects develop anaphylaxis following exposure to BAX 855.

The study may be terminated, if one or more of the following criteria are met:

- The Sponsor decides to terminate the study based upon its assessment of safety.
- The Sponsor decides to terminate the study for administrative reasons.

2.6 Study Assessments

See Section 21.3: Schedule of Study Procedures and Assessments, of the Clinical Study Protocol for information on study assessments.

2.7 Data Monitoring Committee

A Data Monitoring Committee (DMC) will not be used for this study as the expected related AEs in this study are anticipated to be similar to those of the licensed product ADVATE (of which the core protein is identical to that of BAX 855). Additionally, the safety is not expected to differ from the safety observed in the BAX 855 pivotal study and the ongoing BAX 855 continuation study (Studies 261201 and 261302, respectively).

3. STUDY OUTCOME MEASURES

3.1.1 Primary Outcome Measures

The primary outcome measure is the presence or absence of any bleedings in the second 6-month study period (Observation Day [ObsDay 183] to ObsDay 364).

3.1.2 Secondary Outcome Measures

3.1.2.1 Efficacy

1. Total, spontaneous, and traumatic ABR, and spontaneous AJBR.
2. Total weight-adjusted consumption of BAX 855.
3. Overall hemostatic efficacy rating at 8 (±1) hours after the initiation of treatment and at resolution of bleed.

4. Number of BAX 855 infusions needed for the treatment of bleeding episodes.
5. HJHS.
6. Intra-, post- and perioperative hemostatic efficacy in case of surgery.
7. Intra- and postoperative blood loss in case of surgery.

3.1.2.2 Safety

1. Occurrence of AEs and serious adverse events (SAEs).
2. Clinically significant changes in vital signs and clinical laboratory parameters (hematology, clinical chemistry, and lipids).
3. Inhibitory antibodies to FVIII, and binding antibodies to FVIII, BAX 855, polyethylene glycol (PEG), and Chinese hamster ovary (CHO) protein.

3.1.2.3 Patient Reported Outcomes

1. Physical domain and component scores of the SF-36 Health Survey questionnaire.

3.1.2.4 Pharmacokinetics

1. BAX 855 PK parameters based on FVIII activity at baseline and steady state, if applicable:
    a.
        i. Area under the plasma concentration versus time curve from 0 to infinity ($AUC_{0-\infty}$).
        ii. IR at C_{max}.
        iii. Time to half life ($t_{1/2}$) in plasma.
        iv. Mean residence time (MRT) in plasma.
        v. Clearance (CL).
        vi. Maximum plasma concentration (C_{max}).
        vii. Time to maximum concentration (T_{max}) in plasma.
        viii. Volume of distribution at steady state (V_{ss}).
    b. Incremental IR at 15-30 minutes post-infusion over time.

3.1.3 Exploratory Outcomes Measure

1. TGA parameters:
    a. Lag time.
    b. Time to peak thrombin generation.
    c. Peak thrombin generation.
    d. ETP.
2. Bleed and pain severity scores as measured by the Haemo-SYM questionnaire.
3. HRQoL as assessed using EQ-5D and mental domain and component scores of the SF-36.

4. Health resource utilization.

4. ANALYSIS SETS

4.1 All Subjects Enrolled Set (ENR)

The all subjects enrolled set (ENR) is to contain all subjects that signed informed consent.

Information on whether a subject signed informed consent is obtained from the *Informed Consent* electronic case report form (eCRF) panel.

4.2 Safety Analysis Set (SAS)

The safety analysis set (SAS) is to comprise all subjects in the ENR with at least one BAX 855 infusion. All safety analyses will be performed on the SAS.

Information on dosing with BAX 855 is obtained from the following eCRF panels:

- *Study Infusion (both ERT Integration and Missed and on site infusions)*.
- *Infusion for Determination of Incremental Recovery.*
- *Infusion for PK Assessment.*

4.3 Full Analysis Set (FAS)

The Full Analysis Set (FAS) is to comprise all subjects who were randomized to one of the two treatment arms and treated prophylactically for any period of time.

4.4 Per-Protocol Analysis Set (PPAS)

The Per Protocol Analysis Set (PPAS) is to comprise all subjects in the FAS who:

- Completed the second 6 months (ObsDay 183 to ObsDay 364) of prophylactic treatment. Defined as not having prematurely discontinued from the study.
- Had no major deviations from the protocol affecting the study results.

Major protocol deviations are defined in the Protocol Deviation Plan. Protocol deviations are obtained from the following sources:

- IQVIA Clinical Trial Management System (CTMS).
- Programmatical testing by IQVIA Biostatistics.
- The end of study, final Data review/analysis set assignment meeting.

During the course of the study, data review meetings (for data cleaning) will be held on a regular basis. During these meetings the quality of the data will be assessed.

Prior to performing any final analysis as set out in this Statistical Analysis Plan (SAP), a meeting will be held discussing the impact of any major protocol deviation on the analysis. If a subject presents with a major protocol deviation, it is not in itself cause to exclude the subject from the PPAS. Only at the protocol deviation discussion meeting will the decisions be made on whether a subject should be excluded from the PPAS or not, taking the major protocol deviation information into consideration. The meeting should be attended by participants from at least Biostatistics and Medical.

Below is a list of possible major deviations that may influence the study results, which will be discussed at the protocol deviation discussion meeting:

- Subjects less than 75% exposed to BAX 855 as derived in Section 6.6: Measurements of Treatment Compliance.
- Subjects less than 75% compliant to planned dosing regimen as discussed in Section 6.6: Measurements of Treatment Compliance.
- Use of expired or temperature compromised IP.
- Use of a Pegylated product other than BAX 855.

4.5 Pharmacokinetic Analysis Set (PKAS)

The PK Analysis Set (PKAS) is to consist of all subjects in the SAS that have at least one quantifiable post-dose FVIII activity level without major protocol deviations or events with potential to affect the PK analysis. Events with the potential to affect the PK analysis include, but is not limited to are:

- For the intial PK assessment, a washout period <72 hours.
- Initial PK infusion outside the range of 60±5 (IU/kg).
- Interruption of initial PK infusion.

These events as well as protocol deviation information will be discussed at the protocol deviation discussion meeting (at which the ananlysis sets are also assigned). Decisions regarding the exclusion of a subject from the population will be documented in the analysis set assignment sheet.

4.6 Surgery Analysis Set (SGAS)

The surgery analysis set is to consist of all subjects in the FAS that underwent some form of surgery (including dental) during the course of their PROPEL participation as recorded on the eCRF.

5. STATISTICAL CONSIDERATIONS

5.1 Interim Analysis

No interim analysis is planned for this study.

5.2 Final Analysis

The final planned analysis identified in this SAP will be performed by IQVIA Biostatistics following Baxalta's (now part of Shire) authorization of this SAP and Database Lock.

The final analysis will be performed on a clean database:

- All outstanding data issues and queries resolved.
- All irresolvable data issues documented in the Data Handling Report (DHR) from Data Management.
- All coding of medications and AEs completed.
- SAE reconciliation completed.
- Flagging of clinically significant changes in vitals signs by Baxalta (now part of Shire) completed.
- All reconciliation of vendor data with eCRF data completed successfully.

It should be noted that all verbatim text from the eCRF presented in any outputs, will be presented verbatim with no manual hard coding corrections for such data.

5.3 Reference Start Date, Surgery Day and Observation Days

5.3.1 Reference Start Date

Reference start date is defined as the day of the subject's first BAX 855 PK-guided prophylactic infusion, after enrolment in the 261303 protocol (henceforth referred to as the PROPEL study) and will be referred to as ObsDay 1. Subjects who discontinue study participation prior to receiving any BAX 855 prophylactic administration in the PROPEL study are not to have a reference start date.

5.3.2 Surgery Day

Surgery day (SDay) is a relative study day, calculated per surgical procedure for each subject as applicable. The day on which the subject receives pre-surgical loading dose is defined as SDay 1 for each respective surgery. SDay will then increase for every day after SDay 1 until the day before the subject resumes PK-guided prophylaxis in the PROPEL study.

To distinguish between SDays of different surgeries per subject, and additional variable will be assigned, indicating a specific surgery as the i'th chronologic surgery for the subject.

Surgery Day = (Date of Event – Date of SDay 1)

Where date of event is any surgery related assessment or measurement performed.

For example, consider a subject that had two surgeries during the study and received pre-surgical loading dose on the same day as the surgery procedure. For the 1st surgery, the subject resumed regular PK-guided prophylaxis 3 days after the procedure and for the 2nd surgery, 4 days after the procedure. The subject would then have SDay running from 1 to 2 for the 1st surgery and SDay running from 1 to 3 for the 2nd surgery.

Surgery days/periods will be excluded for efficacy analyses purposes as if the subject left the study for surgery and returned to the study once regular PK-guided prophylaxis was resumed (as was the actual case for the 261302 study).

5.3.3 Observation Day

ObsDay is calculated from the Reference Start Date, and will be used to present the relative start and stop day of assessments and events not related to surgery.

- If the date of the event is prior to the Reference Start Date then:

ObsDay = (*Date of Event – Reference Start Date*)

- If the date of the event is on or after the reference start date then:
  - If a subject has no surgeries between Reference Start Date and the date of event then:

$$ObsDay = (Date\ of\ Event - Reference\ Start\ Date) + 1$$

- If a subject has one or more surgeries between reference start date and the date of event then:

$$ObsDay = (Date\ of\ Event - Reference\ Start\ Date) + 1 - (Total\ Number\ of\ SDays\ preceding\ Date\ of\ Event)$$

In the situation where the assessment/event date is partial or missing, observation day and corresponding durations will not be calculated.

5.4 Observation Periods and Annualized Bleeding Rate

Two types of observation period will be defined for use within the analysis and reporting of this study namely the observation period of efficacy (OPE), and the extended observation period of efficacy (eOPE).

5.4.1 Observation Period of Efficacy

- The observation period for efficacy (OPE) measured in days, is calculated as:

$$OPE(days) = Observation\ day\ of\ last\ BAX\ 855\ Prophylactic/IR\ Treatment + Last\ Assigned\ Infusion\ Frequency\ (days)$$

Where last assigned infusion frequency is the last dosing frequency assigned to the subject under a dose change or, in the absence of any dose changes, it is the assigned dose frequency at the start of the study.

- The OPE in (years) is calculated from the OPE (days) as:

$$OPE(years) = \frac{OPE(days)}{365.2425}$$

- The OPE (weeks) is calculated from the OPE (days) as:

$$OPE(weeks) = \frac{OPE(days)}{7}$$

- The OPE (months) is calculated from the OPE (years) as:

$$OPE(months) = OPE(years) \times 12$$

5.4.2 Extended Observation Period of Efficacy

The protocol requires that for subjects that did not complete the full 364 observation days, this study should also include any post-discontinuation (post-PROPEL), bleed information provided by either the subject, or from another BAX 855 study, to augment the bleed data for the subject's missing observation period in PROPEL. To facilitate the use of this post-PROPEL data in the efficacy analysis, the extended observaion period of efficacy (eOPE) is defined:

- The eOPE measured in days, is calculated as:

$$eOPE(days) = OPE\ (days) +$$
(Imputation Start Date - Stop Date of post-PROPEL bleed data)

  Where Stop Date of post-PROPEL bleed data is defined as the minimum of:
  - Date corresponding to subject's ObsDay 364 in the PROPEL study.
  - Actual recorded date of the last bleed data provided for the subject as post-PROPEL bleed data.

  Imputation start date is defined as the maximum of:
  - The day immediately following the date corresponding to OPE (days).
  - The day immediately following the stop date of post-PROPEL bleed data.
  - Date corresponding to subject's ObsDay 183.

- The eOPE in (years) is calculated from the eOPE (days) as:

$$eOPE(years) = \frac{eOPE(days)}{365.2425}$$

5.5 Handling of Missing, Unused, and Spurious Data

Except for the below specified, missing data will not be imputed.

5.5.1 Annualized Bleeding Rate

For all subjects who prematurely discontinued from the study (i.e., before ObsDay 364), and who refuse to provide data on bleeds for the remaining time till ObsDay 364, the number of bleeds (and hence the ABR), will be imputed for the second 6-month period, using Multiple Imputation techniques as described below. The ABR for a subject is calculated as the number if bleeds devided by the observation period under consideration (expressed in years).

The number of bleeds during the missing observation period in PROPEL, will be imputed for subjects taking into account, additional post-PROPEL bleeding information that is provided for the subject. Post-PROPEL bleeding information obtained for a subject (either by the subject or from another BAX 855 study), will be treated as if observed within PROPEL before the imputation procedures.

For simplicity, the imputation process is described below for a single subject (since the imputation will be performed on a subject specific basis), focussing on the period of interest for the primary endpoint (2nd 6-month period). The imputation process is described in step-by-step manner.

5.5.1.1 Primary Endpoint Imputation

The unobserved period (which is subject specific), is defined as the subject's missing observation period in PROPEL for which there is no post-PROPEL bleed information provided.

Step1: Fitting the model

- A subject specific Negative Binomial model will be fitted. The dependent variable (left-side of the model equation), is the number of bleeds in the subject's unobserved period after ObsDay 182, taken from all subjects in the same treatment arm (low level or high level), as the subject being imputed. The offset will be the logarithm of the duration (in days), of the unobserved period for the subject (LUP). Covariates (model variables) will be stratum category, race, age at baseline and total number of bleeds observed per subject (OB), calculated for all subjects in the same treatment group of the subject for imputation.

- It is desired to avoid using bleeds in the endmost observation period as part of the covariates since the number of bleeds observed in other subjects at that time might be very low or even zero. Therefore OB, is measured in the range from ObsDay 92 up to the minimum of:
  - Last ObsDay for subject being imputed.
  - ObsDay 329.
- The following example SAS® code can be utilized:

```
Proc Genmod Data = <Dataset>;
  Class <Stratn> <Racen>;
  Model <UB> = <Stratn> <Racen> <BAge> <OB> / Dist = Negbin
        Offset = <LUP> Link = log;
  ODS Output ParameterEstimates = <Outdata>
Run;
```

Where <Dataset> represents the input dataset containing all subjects in the same treatment arm as the subject being imputed, who have at least the same amount of ObsDays as the subject being imputed. <UB> represents the number of bleeds during the subject's unobserved period (up to the maximum of ObsDay 329), <Stratn> is the numeric stratum category, <Racen> the numeric race category, <BAge> the age at baseline, <OB> and <LUP> as defined above and <OutData> the output dataset containing the parameter estimates.

Step2: Predicting the Poisson Parameter and Imputing with it

- The subject-specific Poisson parameter will be predicted from the above model fitting results by using the predicted mean number of bleeds during the subject's unobserved period (Mu) as the prediction for the Poisson parameter.
- The number of bleeds for the subject to be imputed, will be for the "imputation period" (days), where the imputation period is defined as:

  Imputation Period (days) = (Date Corresponding to ObsDay 364 – Imputation Start Date)

  Where imputation start date is as defined in section 5.4.2: Extended Observation Period of Efficacy.

- This "imputation period" will be treated/imputed as a Poisson random variate. The following example SAS® code can be utilized to obtain an estimate for the Poisson parameter:

```
Data <ImpSet>;
  Set <Dataset>;

  <Mu> = exp(1*<Intcpt> + <Beta1>*<sStrat> + <Beta2>*<sRace> +
         <Beta3>*<sBAge> + <Beta4>*<sOB> + <LIP>);
  Do i = 1 to 1 000
    <ImpUB> = Ranpoi(1234,mu);
    Iteration = i;
    Output;
  End;
Run;
```

  Where <Impset> represents the resultant dataset containing the 1 000 imputed bleed count values. <Dataset> is the input dataset containing the parameter estimates obtained from fitting the Negative binomial as discussed above and <Mu> our Poisson parameter as defined above. <Beta1>, <Beta2>, <Beta3> and <Beta4> the parameter estimates for <Stratn>, <Racen>, <BAge> and <OB> respectively. <sStratn>, <sRacen>, <sBAge> and <sOB> hold values specific to the subject being imputed, for numeric stratum category, numeric race category, baseline age and observed bleeds from ObsDay92 till last ObsDay for the subject, respectively. <LIP> is the logarithm of the imputation period (days) for the subject being imputed and <ImpUB> is the imputed number of bleeds during the imputation period for the subject.

Step3: Adding of Imputed Values to the Observed Values

The imputed bleed count of the subject is added to the subject's observed bleed count (i.e. the subject's observed bleeds after ObsDay 182), to obtain a bleed count for the complete 2nd 6-month period of the subject.

Complete period bleeds = Observed period bleeds + Bleeds for imputation period

For each subject to be imputed, the 1 000 imputed values will be merged into the full subject dataset, thus creating 1 000 replicates of imputed (complete) data sets (one for each imputation iteration).

Step4: Calculating ABR and Categorization

From this step onward we are working with all the subjects (those imputed and those not needing imputation) in the same dataset (1 000 replicates of them).

ABR is calculated as:

$$ABR = \frac{(Observed\ Number\ of\ bleeds + Imputed\ number\ of\ bleeds)}{Period\ under\ consideration\ in\ years}$$

Where period under consideration is:

- 1 year (365.2425 days) when working with the full year.
- 0.5 years (182 days) when working with the second 6-month period.

For presentations using unimputed ABR:

$$Unimputed\ ABR = \frac{Number\ of\ bleeds\ observed\ within\ PROPEL}{Period\ under\ consideration\ in\ years}$$

A numeric categorical variable for imputed ABR during the complete planned treatment period will be derived as follows:

- Category 1: ABR = 0.
- Category 2: ABR > 0.

Step5: Analysis of Imputed Data Sets

Chi-squared statistics with continuity correction should be calculated for each of the thousand complete datasets on the ABR categorical variable with treatment arm as fixed effect. The following SAS® code can be used:

```
Proc Freq Data = <Dataset>;
  By <Iter>;
  Tables <ABRCat>*<Trt> / chisq alpha = 0.05 relrisk riskdiff expected;
  exact or;
  Ods Output Chisq = <Outdata>;
Run;
```

Where <Dataset> is the input dataset containing the 1 000 iterations of the completed

data, <Iter> the iteration number, <ABRCat> the numeric ABR category variable, <Trt> the treatment arm and <Outdata> the output dataset containing the continuity adjusted chi-squared statistics.

Step6: Combining of Statistical Results

An approximately Gaussian test statistic will be derived as the square root of the chi-squared statistic with continuity correction and 1 degree of freedom, with the sign set according to the direction of the effect (proportion higher in treatment arm one [High level] than in treatment arm two [Low level]; zero if equal). That is, if the risk difference of the High Level Arm minus the Low Level arm provided by SAS® is larger than naught then the sign to retain will be positive and vice versa.

This needs to be done so the requirements of Rubin's rules are met and the SAS procedure PROC MIANALYZE can be used.

The resultant 1 000 approximately Gaussian test statistics will be summarized using the SAS® procedure MIANALYZE. SAS® code similar to the below can be utilized:

```
Proc MIanalyze data=<Dataset>;
  Modeleffects <NormStat>;
  Stderr <NormSterr>;
  Ods Output ParameterEstimates = <Outdata>;
Run;
```

Where <Dataset> represents the input dataset containing the approximately Gaussian statistics, <NormStat> and <NormSterr> the approximately Gaussian statstics and standard error of 1 respectively and <Outdata> the output dataset containing the overall estimate, 95% confidence interval and corresponding P-value.

Step7: Back Transformation

The resulting overall estimate and 95% confidence interval should be back transformed (due to using a logarithmic link function when fitting the Negative Binomial model), by applying the following calculation:

$$BackTransformed\ value = exp[(Value)]$$

5.5.1.2 Sensitivity Analysis

For the sensitivity analyses, the same imputation procedure as described above will be applied with the Poisson parameter being artificially increased by 10%, 20%, 40% and 80% for all subjects imputed, regardless of their respective treatment arm. Imputation will also be performed as described in Steps one through seven, but with the post-PROPEL bleed data removed.

5.5.1.3 Secondary Endpoint Imputation

For spontaneous bleeds, traumatic bleeds and spontaneous joint bleeds during the 2nd 6-month period, the same procedure as described for the primary endpoint imputation will be applied in separate models.

For bleeds during the full 12-month period, a similar imputation procedure will be applied with the difference being that no restriction on bleeds such as having to be after ObsDay 182 will be made.

The same procedure will be used to impute spontaneous bleedings, traumatic bleedings, and spontaneous joint bleedings in separate models.

5.5.2 Exposure

For the purpose of calculating weight adjusted consumption of BAX 855, missing body weight (as obtained from the *Vital Signs* eCRF panels), for a subject will be imputed with the last available measurement prior to the specific infusion. For PK parameter analysis, missing start time of infusion is a major protocol deviation and no imputation of PK infusion start time for PK parameter analysis will be performed.

Should the start time of an infusion be known and the end time of an infusion be unknown, the end time of the infusion will be imputed as five minutes after the start time of the infusion for the purpose of PK parameter calculation.

Should the end time of an infusion be known and the start time of an infusion be unknown, the start time of the infusion will be imputed as five minutes prior to the end of the infusion for the purpose of PK parameter calculation.

No imputations on infusion dates will be performed, i.e., imputations should only be performed on infusion times.

5.5.3 Adverse Events

- Causality:
  A missing relationship to study medication will be considered "worst case", as "related".
- Severity:
  - In the event that the subject reported more than one AE under the same preffered term (PT), where one has an 'unknown' severity and the other a non-missing severity is recorded as 'severe', the missing severity will be imputed as 'severe'.
  - In the event that the non-missing severity is 'mild' or 'moderate', the 'unknown' severity is to remain.

5.6 Definition of Baseline

Baseline is defined as the last non-missing (scheduled or unscheduled) measurement obtained prior to the reference start date discussed in Section 5.3: Reference Start Date, Surgery Day and Observation Days. If the date of the last non-missing assessment and the reference start date coincide, the assessment will be considered as baseline.

The following efficacy items will be making use of Baseline:

- Difference in SF-36 physical domain and component change scores from baseline to completion between treatment arms.
- Difference in change of days of physical activity participation from baseline to completion between treatment arms.
- Difference in the change in healthcare resource utilization from baseline to completion between treatment arms.
- Within treatment arm change in the HJHS total score from Baseline to Completion.
- Within treatment arm change and between treatment arm change in Haemo-SYM total score as well as bleed and pain severity between baseline and completion.
- Within treatment arm change and between treatment arm change in EQ-5D utility total score as well as VAS score between basleine and completion.

5.7 Definition of Visit Windows

All data should be presented by nominal visit date and name as recorded on the eCRF (in chronological order). Visits will not be reassigned from the recorded nominal visit to any other visit based on dates.

5.8 Changes from the Planned Statistical Analysis in Protocol

The Clinical Study Protocol states that the correlations between average coagulation parameters (TGA parameters: lag time, time to peak thrombin generation, peak thrombin generation, ETP and FVIII trough levels) and ABR will be assessed/displayed by boxplots. For consistency with the presentation in the 261302 continuation study, linear regression plots with 95% CIs will be used instead.

The Clinical Study Protocol states that IR at 15-30 minutes post-infusion will be calculated based on FVIII activity at baseline and steady-state. Instead, IR at C_{max} will be determined for PK assessment visits. Incremental recovery over time at scheduled IR visits will be preseted for IR at 15-30 minutes post-infusion.

In addition to the analysis described in the protocol, a listing and corresponding summary table of IR resulting from the use of 3 000 IU vials will be presented. The table will only contain descriptive statistics of IR at 15-30 minutes post-infusion by scheduled visit.

5.9 Statistical Tests

The default significance level will be 5%; CIs will be 95% and all tests should be two-sided, unless otherwise specified in the description of the particular analysis.

P-values obtained from statistical inference tests should be presented using four decimal places.

Unless otherwise specified the default summary statistics for quantitative variables will be as follows:

- The number of subjects in each category (n).
- Mean.
- Standard deviation (SD).
- First quartile (Q1).
- Median.
- Third quartile (Q3).
- Inter-quartile range (IQR); calculated as Q3 – Q1.
- Minimum.
- Maximum.

The number of subjects (n) with missing or unavailable results for quantitative variables will be presented as "Not reported" where applicable. A "Not reported" category should only be presented should there be unavailable results. No distinction based on the reason for unavailable results will be made within any presentations.

If the original data has N decimal places (as derived from the raw data) (i.e., decimal precision [N]), then the summary statistics are to contain the following decimal places (with a maximum of three decimals):

- Minimum and maximum: N.
- Mean, median, Q1, Q3 and IQR: N + 1.
- SD and CI: N + 2.

For qualitative variables the number (n) and percentage (%) of subjects in each category will be the default summary presentation. Unless otherwise specified, percentages should be calculated relative to the total number of subjects in the relevant analysis set and treatment arm as described in the latest version of the Output Templates. For unavailable assessments a "Not reported" category should be presented. A "Not reported" category will only be presented if applicable. The "Not reported" category should be presented with a percentage so that the sum of the percentages of all categories, including the "Not reported" category, totals 100%. No distinction based on the reason for unavailable results will be made in any presentations.

All values should be rounded using the SAS® function ROUND. All calculated percentages should be presented using one decimal place.

The following data handling will be applied for PK assessments/analysis.

All PK concentrations/FVIII activity levels will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of the amount of significant figures or decimals the data carry. Derived pre-infusion-corrected concentrations will be rounded to the same decimal precision as the source data for presentations in listings and calculation of descriptive statistics. Unrounded derived PK data will be considered the source data for the calculation of descriptive statistics and the statistical analysis. For most derived PK parameters, three significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (eg, C_{max}) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (eg, T_{max}) are to be reported with the same precision as the actual elapsed sampling time value of the source data.

For the reporting of descriptive statistics for PK data, the mean, geometric mean, median, Q1, Q3, IQR, SD, and CIs are to be presented to 1 digit more precision. The minimum and maximum are to be presented to the same precision. Coefficient of variation (CV%) and geometric CV% are always to be reported to 1 decimal place.

5.10 Common Calculations

For quantitative measurements, change from baseline is calculated as:

Change from Baseline at Visit X = Test Value at Visit X – Baseline Value

Change from pre-infusion is calculated as:

Change from pre-infusion at Visit X = Test Value at Visit X post-infusion – Test Value at Visit X pre-infusion

5.11 Multicenter Studies

This study is conducted by multiple Investigators at multiple centers internationally.

Unless specified otherwise, all summaries should be produced overall and will not be summarized by center as the number of subjects per study site is too small.

5.12 Examination of Subgroups

The following subgroups will be utilized in analyses as indicated in the latest version of the Output Templates as well as the various sections to follow:

- Stratum, as derived from the pre-study ABR and pre-study treatment type, captured on the Hemophilia A Treatment History eCRF panel:
  - Pre-study prophylaxis treatment with ABR <5.
  - Pre-study prophylaxis treatment with ABR ≥5.
  - Pre-study on-demand treatment.

- Age groups (years) (per different regulatory standards, resulting in overlapping groups), using age at informed consent as obtained from the Demographics eCRF panel:
  - European Medicines Agency (EMA):
    - European (EU) Age Group ≥12 to <18.
    - EU Age Group ≥18.
  - Food and Drug Administration (FDA):
    - United States (US) Age Group ≥12 to <17.
    - US Age Group ≥17.
- Race as obtained from the Demographics eCRF panel:
  - Asian.
  - Black of African American.
  - Native Hawaiian or other Pacific Islander.
  - White.
  - Other.

5.13 Categorization of Outcome Variables

The following categorization of outcome variables will be used in the analyses as indicated in the latest version of the Output Templates and in the following sections as applicable. Definitions for the below categories are provide in Section 7.1.2: Bleeding Episodes:

- Geographical location:
  - US.
  - Europe.
  - Asia Pacific (APAC).
- Bleed type as obtained from the Bleeding Episodes eCRF panels:
  - Spontaneous/Unknown Bleeds.
  - Injury related bleeds.
- Bleed severity as obtained from the Bleeding Episodes eCRF panels:
  - Bleeds of minor severity.
  - Bleeds of moderate severity.
  - Bleeds of major severity.
- Bleed location as obtained from the Bleeding Episodes eCRF panels:
  - Joint bleeds.
  - Non-joint bleeds.

- Bleed timing as derived using the bleed dates from the Bleeding Episodes eCRF panels:
  - Weekday bleeds.
  - Weekend bleeds.

  Also:
  - Morning bleeds.
  - Afternoon bleeds.
  - Evening bleeds.
- Number of bleeds during the study as obtained from the Bleeding Episodes eCRF panels:
- No bleeds during the study.
- At least one bleed during the study.

5.14 Multiple Comparisons/Multiplicity

Not applicable.

6. STUDY SUBJECTS

6.1 Disposition of Subjects

All subjects with informed consent provided will be accounted for in this study.

Each subject is to participate in the study for approximately a year or until premature study discontinuation. A completion/follow-up assessment will be performed for each subject at study exit.

Subject listings will be presented on the following disposition related items using the ENR:

- Subjects transitioning from other BAX 855 studies.
- Subject disposition in general.
- Informed consent with inclusion/exclusion criterion exceptions.
- Protocol deviations.
- Visit dates.
- Analysis sets.

Summary tables will be presented on subject disposition, protocol deviations and analysis sets using the ENR.

The following information items are obtained from the eCRF:

- Informed consent and protocol version under which the subject enrolls onto the study (Informed Consent eCRF panel):
- Inclusion and exclusion criteria met and/or not met (Inclusion/Exclusion Criteria [transitioning subjects] and Inclusion/Exclusion Criteria [New subjects]) eCRF panels).
- Visit dates (Date of Visit eCRF panel).
- Other studies in the BAX 855 program the subject participated in (Demographics eCRF panel).
- Study completion (Completion/Termination eCRF panel):
- AE term and number (Adverse Event eCRF panel).
- Treatment arm assignment including date randomized (Randomization eCRF panel).
- Study medication administrations in the PROPEL study (Study Infusion eCRF panel).

The following derivations will be made based on the eCRF reported results:

- A subject is considered to be enrolled if date of informed consent is present.
- A subject is considered screening failure if they present with a disposition record of Screening failure as recorded on the end of study eCRF.
- A subject is considered to have received PK dose if recorded as such on the infusion for PK assessment eCRF.
- A subject is considered randomized if assigned to one of the two treatment arms as recorded on the Randomization eCRF.
- A subject is considered to have been dosed prophylactically if any study medication administration or part thereof, occurred for the subject with reason of ‘prophylaxis’ as recorded on the infusion eCRF pages or within the subject diary.
- A subject is considered to be completed if the reason for termination indicates the subject completed the study. Otherwise the subject should be considered discontinued. For the first 6-month period, a subject is considered to be completed if not discontinued before or on ObsDay 182. For the second 6-month period, the subject needs to have a disposition or bleed record at or after ObsDay 364.

6.1.1 Protocol Deviations

Protocol deviations should be summarized by age group, site and classification (critical, major or minor) presenting the number of deviations per site and the number of subjects having the particular deviation.

The information on protocol deviations is obtained from the IQVIA CTMS and/or as identified in the data review meeting to be held for determination of the PPAS and PKAS.

Protocol deviations from the CTMS will be coded to standardized categories and provided as part of the CTMS transfer to Biostatistics.

Changes to the procedures or events, which may impact the quality of the PK data, will be considered significant protocol deviations/events and will be described within the clinical study report body text. These changes or events are to include any circumstances that alter the evaluation of the PK. Examples of protocol deviations that are important for PK are provided below. Actions to be taken on some of these are discussed further in Section 9: Evaluation of Pharmacokinetics.

- Sample processing errors that lead to inaccurate bioanalytical results.
- Inaccurate dosing on the day of PK sampling due to administration incidences or lack of compliance to the protocol.
- Dosing time (start and/or stop time of infusion) not available.
- Blood sampling date and time not available.
- Missing PK samples at important phases of the PK profile.
- Inadequate washout period prior to IP administration.
- Interruption of infusion.

Affected data will be evaluated by the pharmacokineticist to determine whether or not they can be included in the PK analysis. Subjects and/or data with important deviations or other data issues that are not included in the PKAS should be reported in listings, along with the reason for exclusion. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered significant protocol deviations for PK analysis. A common example of a non-significant protocol deviation is a deviation from blood collection times.

6.2 Demographic and Baseline Characteristics

Subject listings are planned for the following items using the analysis set indicated:

- Baseline demographics (SAS).
- Previous participation in PROPEL or Baxter/Baxalta studies (ENR).
- Haemophilia A history and blood group information (SAS).
- Target joint specification at screening (SAS).

Summary tables are planned for baseline demographic and characterisics as well as disease and subject characteristics using the SAS, FAS, PPAS and PKAS:

Demographic and baseline characteristics summaries should be presented by (see Section 5.12: Examination of Subgroups):

- Age group.

The following information items are obtained from the eCRF:

- Demographics and previous PROPEL and/or Baxter/Baxalta study participation (Demographics eCRF panel).
- Height and weight at Screening (Vital Signs eCRF panels).
- Information on haemophilia A history, blood group, family history and target joint identification at Screening (Haemophilia A History/Blood Group/Target Joint Identification eCRF panel).

The following information is obtained from the Medical team based on medical histories reported in the *Medical History* eCRF panels:

- Whether a specific medical history can be considered as haemophilia arthropathy.
- Categorization of gene mutation for use in summaries.

The following information is obtained from the central laboratory:

- Hepatitis C virus antibody at Screening.
- Human Immunodeficiency Virus (HIV) results at Screening.

The following derivations will be made based of the eCRF reported results:

- Age at informed consent (years) is calculated as:

  Age at Screening (years) = Year of Reference Start Date – Year of Birth

- Body mass index (BMI) is derived as:

$$BMI(kg/m^2) = Weight(kg) / \left[\frac{Height(cm)}{100}\right]^2$$

- Race will be presented as "Mixed" in summaries if more than one race is selected on the Demographics eCRF panel.
- The number of target joints at Screening will be counted from the eCRF.
- Average ABR based on previous twelve months will be categorized as:
  - <1.
  - 1 to <3.
  - 3 to <5.
  - 5 to <7.
  - 7 to <10.
  - 10 to <20.
  - 20 to <30.
  - 30 to <40.
  - 40 to <50.
  - 50 to <60.
  - ≥60.

A condensed categorization of ABR based on the previous twelve months, corresponding to the stratification of subject will be made as follows:

- ≤5.
- >5.

The presence of haemophilia arthropathy should be determined as present if any medical history is present that can be considered as haemophilia arthropathy, otherwise should be determined as absent.

6.3 Medical History

A subject listing and summary table for medical history will be presented using the SAS.

The following information items are obtained from the eCRF:

- Medical history (*Medical History* eCRF panel).

The medical history summary should be presented by age group (see Section 5.12: Examination of Subgroups).

6.4 Prior and Concomitant Therapies and Medication

Subject listings will be presented for the following items using the SAS:

- Haemophilia A treatment history.
- Prior PEGylated medications.
- Prior and concomitant medications.
- Prior and concomitant non-drug therapies.

No summary tables are planned for presentation of prior and concomitant therapies and medication.

The following information items are obtained from the eCRF:

- Haemophilia A treatment history (Haemophilia A Treatment History eCRF panel).
- Prior PEGylated medication history (Prior Pegylated Medication History eCRF panel).
- Prior and Concomitant Medication and non-drug therapies (Concomitant Medications/Non-drug Therapies eCRF panel).
- Information on AEs and medical histories for which the medication or non-drug therapy has been given (Adverse Events and Medical History eCRF panels).

Prior and concomitant medications, haemophilia A treatment history and prior PEGylated medications are coded using the latest version of the World Health Organization-Drug Dictionary (WHO-DD), which is updated twice a year.

The following derivations will be made based of the eCRF reported results:

- Assignment to prior or concomitant:
  - A medication or non-drug therapy should be assigned as “Prior” if the medication or non-drug therapy stopped prior to first BAX 855 administration in the PROPEL study.
  - A medication or non-drug therapy should be assigned as “Concomitant” if the medication or non-drug therapy:
    - Started after first BAX 855 administration in the PROPEL study; or
    - Started before the first BAX 855 administration in the PROPEL study and ended after first BAX 855 administration in the PROPEL study.
  - A medication or non-drug therapy should be assigned as “Unknown” if missing dates do not allow for assignments based on above rules.
  - Based on the reason for medication or therapy, the actual AE or medical history term will be obtained by linking the information from the respective eCRF panels.

6.5 Extent of Exposure

Subject listings will be presented for the following items using the SAS:

- BAX 855 study infusions (including lots used and interruptions).
- Exposure to BAX 855 study infusions.
- Dose adjustment.
- Postoperative prophylaxis.

Summary tables for exposure to BAX 855 will be presented using the SAS, FAS and PPAS. Summaries will be presented by age group.
The following information items are obtained from the eCRF:

- Study infusion information (Study Infusion eCRF panels).
- Dose adjustment (Change of Dose eCRF panel).
- Postoperative prophylaxis (Postoperative Prophylaxis eCRF panel).
- Body Weight (Vital signs eCRF panels).

Due to the study having two sources of BAX 855 infusion information being captured (subject diaries via third party vendor ERT and the eCRF), the SAS® data tranfered to IQVIA Biostatistics contain duplicate records for the same infusion. When these records are exact duplicates (including dates and times), IQVIA Biostatistics are to handle these

duplicates as such within the Analysis Data model (ADaM) programming. Records that are not exact duplicates, will not be regarded as duplicate records by IQVIA Biostatistics and will be presented.

The following derivations will be made based of the eCRF reported results:

- Infusion duration should be determined as:

Infusion duration = (Infusion Stop Time – Infusion Start Time)

- Body weight-adjusted dose (IU/kg) should be derived as the total units infused (IU) divided by the last available body weight (kg) prior to the infusion. See to Section 5.5: Handling of Missing, Unused, and Spurious Datafor imputation rules to be implemented.
- The total number of infusions is determined as the total count of the number of infusions, regardless of date and time, the subject had. Number of infusions will be determined overall and by reason for infusion as well as by the treatment arm assigned to at the time of receiving the treatment.
- The number of EDs is determined as the number of unique calendar days on which a subject received study medication or part thereof. Multiple infusions on the same day will still be considered as one ED. EDs will be determined overall as well as for each reason a study medication administration is given.
- The observation period for efficacy (OPE) measured in days, in the study for subjects should be determined as provided in Section 5.5.1: Annualized Bleeding Rate.
- The OPE (weeks) should be determined from the OPE (days) as provided in Section 5.5.1: Annualized Bleeding Rate.
- The OPE (months) should be determined from the OPE (days) as provided in Section 5.5.1: Annualized Bleeding Rate.
- The OPE in (years) should be determined from the OPE (days) as provided in Section 5.5.1: Annualized Bleeding Rate.
- The average number of infusions per time period (weeks, months, years) should be determined as the total number of infusions during the full observation period, divided by the duration for the particular time period (weeks, months, years).
- Total dose (IU/kg or IU as applicable) should be determined as the sum of all doses, overall and by reasons for infusion, during the observation period in the current study.

- The average dose per time period (weeks, months, years) should be determined as the total dose (IU/kg or IU as applicable), the subject received during the observation period in the PROPEL study, divided by the duration for the particular time period (weeks, months, years).
- Average dose per bleed is determined as the sum of all doses (IU/kg or IU as applicable) given to treat bleeding episodes, divided by the number of bleeds observed for the particular subject in the current study.

6.6 Measurements of Treatment Compliance

A subject listing (using the SAS) and summary tables (using the SAS, PPAS and PKAS) on compliance.

Treatment compliance will be derived using results and derivations obtained from study exposure as described in Section 6.5: Extent of Exposure.

Treatment compliance will be based on the following:

- Adherence to the study medication administration schedule; and
- Adherence to recommended prophylactic dosing plan.

An infusion will be considered in adherence to the study medication administration schedule if it does not deviate by more than ±8 hours from the PK-guided assigned dosing frequency:

Based on the treatment regimen, time that a subject was not covered by BAX 855 prophylaxis, will be determined. The time in minutes that a subject was not covered by BAX 855 prophylaxis is calculated as the sum of all time periods exceeding the planned infusion interval after a prophylactic infusion.

Time not exposed (minutes) should be set to 0 if the above derivation results in number of days less than 0.

The percentage of time a subject was covered by BAX 855 prophylaxis, should be derived as follows:

$$Time\ Covered\ by\ Prophylaxis\ (\%) = \frac{OPE(Minutes) - Total\ Time\ not\ Covered\ (Minutes)}{OPE(Minutes)} \times 100$$

An infusion is considered to be in adherence to the recommended prophylactic dose if the actual amount infused (IU/kg) is between 90% and 110% of the planned/assigned dose (IU/kg) to be infused. Infusions with actual amount infused not recorded in the eCRF, will be excluded from the compliance calculations.

The number and percentage of infusions in adherence to the recommended prophylactic dosing plan, will be determined for each subject using the overall number of infusions for that subject as denominator.

6.6.1 Handling of Subjects Assigned an Alternating Dose Frequency

Some subjects are assigned an alternating dose frequency. To match any given dose to one of the two alternation options, the actual infusion's dose level (IU/kg) and time passed since last infusion will both be compared to the two alternations assigned. The infusion will then be paired with the alternation option that maches closest to the actual infusion. If such comparison is inconclusive, the planned dose (IU/kg) as recorded in the subject diary will be used to pair the infusion with one of the alternation options.

7. EFFICACY EVALUATION

7.1 Analysis of Primary Efficacy Outcome Measure

The primary efficacy measure is the proportion of subjects with an ABR = 0 per treatment arm during the second 6-month period of the study (ObsDay 183 to ObsDay 364). Other measurements of bleeds are part of the secondary and exploratory outcome measurements as documented in Section 7.2: Analysis of Secondary Efficacy Outcome Measure and Section 11: Exploratory Analyses.

7.1.1 Hypothesis Regarding Primary Efficacy Outcome Measure

The null hypotheses of no difference between the two treatment arms will be tested against a two-sided alternative.

$$H_0: \text{Proportion Low Level subjects with ABR of 0} = \text{Proportion High Level subjects with ABR of 0}$$

versus

$$H_a: \text{Proportion Low Level subjects with ABR of 0} \neq \text{Proportion High Level subjects with ABR of 0}$$

7.1.2 Bleeding Episodes

Subject listings will be presented for the following items using the analysis set indicated in brackets:

- Bleeding episodes treated with BAX 855 including efficacy ratings (FAS).
- Bleeding episodes not treated with BAX 855 (FAS).
- Annualized bleeding rate and interval between bleeding episodes (SAS).
- Course of target joints (SAS).
- Magnetic resonance imaging and ultrasound (SAS).

Summary tables will be presented for the following items using the analysis set indicated in brackets:

- Descriptive statistics on annualized bleeding rate (FAS, PPAS) presented by age group, geographical location and race,.
- Comparisons presented by age group and race on:
  - Annualized bleeding rate overall and for the second 6-month study period (FAS and PPAS).
  - Sensitivity Analysis on ABR during the second 6-month study period (FAS).
- Comparisons presented by age group and race on observed annualized bleeding rate (FAS and PPAS).
- Comparisons presented by age group on:
  - Average coagulation parameters against ABR using the Spearman rank correlation coefficient, both overall and for the second 6-month study period (FAS and PPAS).
  - Reduction on ABR (FAS and PPAS).
  - Descriptive statistics on average interval between episodes [Months] (FAS and PPAS).
  - Bleeding episodes (FAS).
  - Hemostatic efficacy against number of BAX 855 infusions to treat perioperative bleeds (FAS).
- Presented by age group, bleed type, bleed severity, bleed location and bleed timing:
- Characteristics of bleeding episodes treated with BAX 855 (FAS).
- Hemostatic efficacy against number of BAX 855 infusions to treat bleeds (FAS).

Figures will be presented for the following items using the FAS:

- Dot and whisker plot (point and 95% CI) of ABR (by treatment arm).
- Multi bar plot of subject treatment profile with infusions, bleeding episodes and antibody titers.
- Linear regression plot of average observed factor VIII trough levels (IU/dL) against observed ABR.
- Linear regression plot of TGA against observed ABR.

The following information items are obtained from the eCRF:

- Bleeding episodes (Bleeding Episode eCRF panels).
- Target joints (Haemophilia A History/Blood Group/Target Joint Identification and Development of new Target Joints eCRF panels).
- Infusions to treat bleeding episodes and prophylactic infusions prior to bleeds (Study Infusion eCRF panels).
- Ultrasound (Ultrasound eCRF panel).

The following derivations will be made based of the eCRF reported results:

- The following anatomical bleeding sites are considered to be joints:
  - Left wrist.
  - Right wrist.
  - Left elbow.
  - Right elbow.
  - Left shoulder.
  - Right shoulder.
  - Left hip.
  - Right hip.
  - Left knee.
  - Right knee.
  - Left ankle.
  - Right ankle.
- An identified joint will be considered a target joint if:
  - The joint is identified as a target joint from either the Haemophilia A History/Blood Group/Target Joint Identification or the Development of new Target Joints eCRF panel.

  - There were at least four spontaneous bleeding episodes within a consecutive 6-month period in the joint.
  - A joint will cease to be considered a target joint if identified in the eCRF with less than four spontaneous bleeds within a consequtive 6-month period in the joint.
- A bleeding site will be considered a target joint if the specific joint is considered a target joint at the time of the bleed.
- A bleeding site will be considered a non-target joint if the specific bleed is not considered a target joint at the time of the bleed. The bleeding site will still be considered as a joint.
- A bleed will be considered an injury related bleed if the cause is indicated as "Injury".
- A bleed will be considered a spontaneous bleed if the cause of the bleed is identified as "Spontaneous" or "Unknown" in the eCRF.
- A bleed will be considered a major bleed if the severity is indicated as "Major".
- A bleed will be considered a moderate bleed if the severity is indicated as "Moderate".
- A bleed will be considered a minor bleed if the severity is indicated as "Minor".
- A bleed will be considered a weekday bleed if the bleed occurred on a Monday, Tuesday, Wednesday, Thursday or Friday.
- A bleed will be considered a weekend bleed if the bleed occurred on a Saturday or Sunday.
- A bleed will be considered a morning bleed if the bleed occurred between 04:00 and 11:59.
- A bleed will be considered an afternoon bleed if the bleed occurred between 12:00 to 17:59.
- A bleed will be considered a night bleed if the bleed occurred between 18:00 and 03:59.
- A bleed is considered to have occurred at an unknown time if the time of a bleed is not available.

- Time since last prophylactic infusion in hours should be derived as:

$$Time\ (h) = (Date/Time\ of\ Bleed - Start\ Date/Time\ of\ Infusion) / (60 \times 60)$$

where the start date/time of infusion refers to the last prophylactic infusion received (other than to treat a bleed) prior to the start of the current bleed.

Time since previous bleed should be derived as:

Time (h) = (Date/Time of Bleed – Start Date/Time of Infusion) / (30×24×60×60)

- The average interval between bleeding episodes (months) determined as:

$$Average\ Interval\ Between\ Bleeding\ Episodes(Months) = \frac{\sum(Start\ date\ of\ Bleed - End\ date\ of\ Previous\ bleed)}{Number\ intervals\ observed} \times \frac{12}{365.2425}$$

- A bleed will be considered as treated with BAX 855 if at least one infusion linked to the particular bleed is present in the Study Infusion eCRF panels. Infusions to "Maintain Hemostasis" will not be summarized as part of treatment for bleeding episodes.
- The number of bleeds per subject overall and by location (target joint, non-target joint, joint and non-joint), causality (spontaneous/unknown and injury) and severity (minor, moderate and major) should be determined as the count of unique bleeds in each category a subject had during the observation period.
- Annualized bleeding rate (ABR) should be derived as provided in Section 5.5.1: Annualized Bleeding Rate. Categorized ABR (ex. AJBR, Severe ABR etc.) should be derived in a similar manner.

The proportion of subjects with an ABR = 0 in the second 6-month study period (ObsDay 183 to ObsDay 364), will be analyzed and compared between the two treatment arms using a chi-square test with continuity correction at a two-sided 5% (95% confidence) level of significance. The following SAS® code can be used for this analysis:

```
Proc Freq Data = <Dataset>;
  tables <Response>*<Treatment> / chisq alpha = 0.05 relrisk riskdiff
  expected;
  or;
  ODS Output chisq = <Outdata>
run;
```

where <Dataset> refers to the input dataset, <Response> the assignment of subjects between achieving an ABR = '0' or not, in the second 6-month period (ObsDay 183 to ObsDay 363) in binary numeric format (with subjects reaching ABR = 0 being assigned a

'1' [success]), <Treatment> the assigned treatment arm and <Outdata> the output dataset containing the inferential statistics to be presented in the summary tables.

Bleeds recorded in the observation period, will be used regardless of compliance with BAX 855 infusions planned per the Protocol.

The analysis of this data involves the use of a multiple imputation technique on a transformation of this data. See Section 5.5: Handling of Missing, Unused, and Spurious Data. This is the primary analysis for the PROPEL study.

The primary analysis will be repeated as a sensitivity analysis with the following alternative imputations:

- Standard uninflated imputation (excluding regular post-PROPEL bleeds).
- Imputed bleeds with the mean inflated by 10%.
- Imputed bleeds with the mean inflated by 20%.
- Imputed bleeds with the mean inflated by 40%.
- Imputed bleeds with the mean inflated by 80%.
- Worst case bleed imputation (See Section 5.5: Handling of Missing, Unused, and Spurious Data).

The proportion of subjects with total ABR <2, spontaneous ABR <2, Spontaneous ABR = 0, spontaneous AJBR <2 and spontaneous AJBR = 0, for the second 6-month period (ObsDay 183 to ObsDay364) as well as the full 12-month period treatment period (ObsDay 1 to ObsDay 364), will be analyzed in the same manner as the primary efficacy outcome. The sensitivity analysis described above for the primary efficacy outcome, will not be applicable to the secondary efficacy outcomes.

The total ABR, injury related ABR, spontaneous ABR and spontaneous AJBR, will be analyzed using a generalized linear model fitting a negative binomial distribution with logarithmic link function for the second 6-month period (ObsDay 183 to ObsDay 364) as well as the full 12-month observation period (ObsDay 1 to ObsDay 364). Separate Negative Binomial models will be used for these two time periods. The model is to include the treatment arm assigned (low level or high level), Stratum and race as fixed effects, age at baseline as continuous covariate and the logarithm of the OPE in years as an offset. The following SAS® code can be used to perform the analysis:

```
Proc Genmod Data = <Dataset>;
```

```
  Class <Treatment> <Strat> <Race> (param=ref ref=first);
  Model <Bleeds> = <Treatment> <PREABR> <Baseline_age> <Race> / type3
  dist = negbin link = log offset = <log_OPE>;
  lsmeans <treatment> / bylevel om CL;
  ODS OUTPUT LSMEANS = <Outdata>;
Run;
```

where <Dataset> refers to the input dataset, <Treatment> the assigned treatment arm, <STRAT> to the Stratum category, <Race> to the subject's race, <Bleeds> the number of bleeds during the observation period, <Baseline_age> to the subject's age at baseline, <log_OPE> the logarithm of the OPE in years and <Outdata> the output dataset containing the inferential statistics to be presented in the summary tables. Point estimates and confidence intervals obtained from the generalized linear model should be anti-logged prior to presentation.

A multiple imputation technique will be used for incomplete observation periods in the same manner as utilized for the primary analysis (See Section 5.5: Handling of Missing, Unused, and Spurious Data). This is the secondary analysis for the PROPEL study.

The potential correlation between ABR and the pre-infusion average FVIII trough levels as well as the average of the TGA trough results .(lag time, time to peak thrombin generation, peak thrombin generation and ETP) will be assessed using linear regression plots with 95% confidence bands and the Spearman rank correlation coefficient for the first 6-month treatment period (ObsDay 1 to ObsDay 182), the second 6-month study treatment period (ObsDay 183 to ObsDay 364) and overall (The full 12-month period [ObsDay 1 to ObsDay 364]). As described in Section 9.1: FVIII Activity and TGA Data, FVIII trough levels will be calculated exactly to the end of the subjects' planned infusion interval; however, trough samples collected outside of ±16 hours of the planned infusion interval, will be excluded. For TGA results, trough levels for each available visit will be included for the calculation of the average by assay if the sample was collected ±2 hours of the planned infusion interval. Trough levels taken within ±16 hours of the planned infusion interval will be used for this correlation test.

The following SAS® code can be used to perform the analysis:

```
Proc Corr data  = <Dataset> Spearman;
  Var <Parameter1>;
  with <Parameter2>;
  title "Correlation coeficients";
  ODS Output  = <Outdata>
Run;
```

where <Dataset> refers to the input dataset, <Parameter1> the first parameter to be checked for correlation, <Parameter2> the second parameter to be checked for correlation and <Outdata> the output dataset containing the inferential statistics to be presented in the summary tables. Please note that the two variables being checked for correlation must be sorted/ranked from low to high before using the SAS procedure.

Where applicable, the 95% CI on the median will be determined using the distribution-free CI for the 50th percentile from the SAS® UNIVARIATE procedure.

He protocol states that for subjects that leave the PROPEL study before completing the full second 6-month period (defined as ObsDay 364), subjects may provide bleeding data for the remaining days up to the end of the full 6-month perdiod (ObsDay 364). There where two subject cases identified which fits this description in PROPEL:

- Subjects transitioning from PROPEL to the Baxalta Continuation study before ObsDay 364.
- Subjects leaving the study before ObsDay 364 but not transitioning to another Baxalta study.

The appropriate file notes have been put in place describing this process. Details of bleed information inclusion into the PROPEL analysis (primary, secondary and exploratory) is given below.

7.1.2.1 Subjects Prematurely Transitioned to the Baxalta Continuation Study

Bleed data for the period from transitioning to the Baxalta Continuation study up to the nominal ObsDay 364 will be obtained in the form of a RAW data export from the Baxalta Continuation study. This transfer will be filtered to contain only the applicable subject numbers identified as having transitioned too early.

The following fields/variable will be utilized for these subjects from the Baxalta Continuation study:

- Unique subject number (for matching across studies).
- Bleed cause (Spontaneous, unknown, injury related).
- Bleed type (Joint, non-joint).
- Onset date of bleed.
- End date of bleed/Ongoing.

- Anatomical bleeding site.
- Severity of bleed.
- Treatment administered for bleed (BAX 855, other: specifiy, none).
- If treated with BAX 855:
- Efficacy rating.
- Infusion date/time.
- Amount infused (IU/kg).

This data will be incorporated into to the SDTM database with flag or category added that would enable the identification of this data as having its source post-PROPEL. For the statistical analyses (primary, secondary and exploratory), this data will be treated as would have been if recorded during PROPEL itself (i.e. observed data).

7.1.2.2 Subjects Prematurely Leaving PROPEL Without Transition to Other Baxalta Study

These subjects will be approached requesting their willingness to provide information regards their bleeding status for the time from leaving PROPEL up to at least nominal ObsDay 364. Should the subject consent, the subject information will be incorporated into the PROPEL RAW data base in one of the following ways:

- If the subject confirms no bleeding episodes occurred during the enquired period, it will be entered as such on the Completion/Termination eCRF page.
- If the subject reports bleeding episodes, the following will be requested from the subject for entering on the Bleeding Episode eCRF pages:
  - Bleed cause (Spontaneous, unknown, injury related).
  - Bleed type (Joint, non-joint).
  - Onset date of bleed.
  - End date of bleed/Ongoing.
  - Anatomical bleeding site.
  - Severity of bleed.

No further bleed related information such as treatment provided for the bleeds will be collected as it beyond the scope of the PROPEL protocol. The data collected for these subjects will be flagged to enable the identification of it as being collected post-PROPEL. For the statistical analyses (primary, secondary and exploratory), this data will be treated as if captured during the PROPEL study (i.e. observed data).

7.2 Analysis of Secondary Efficacy Outcome Measures

The following secondary efficacy outcome measures are discussed in Section 7.1.2: Bleeding Episodes:

- Total, Spontaneous, and Injury Related (Traumatic) ABR, and Spontaneous AJBR.
- Overall hemostatic efficacy rating at 8 hours (±1 hour) after initiation of BAX 855 infusion for the treatment of the bleed as well as at the resolution of the bleed.
- Number of BAX 855 infusions needed for the treatment of bleeding episodes.
- Intra-, post- and perioperative hemostatic efficacy in case of surgery.
- Intra- and postoperative blood loss in case of surgery.

The following are the other secondary efficacy measures that are discussed in this section:

- HJHS questionnaire.
- Haemo-SYM questionnaire.
- Physical domain and component scores of the SF-36 questionnaire.
- EQ-5D questionnaire.
- Healthcare resource utilization (as recorded in the subject diaries).
- Subject physical activity levels.
- The total weight-adjusted consumption of BAX 855 for each treatment arm.

Subject listings will be presented for the following items using the SAS:

- HJHS questionnaire.
- Haemo-SYM questionnaire
- SF-36 questionnaire.
- EQ-5D questionnaire.
- Health resource usage and events.
- Physical activity.

Summary tables containing descriptive statistics and comparisons, using the Wilcoxon signed rank and Mann-Whitney U tests, will be presented on the following items using the FAS:

- The HJHS questionnaire.
- The Haemo-SYM questionnaire.
- The SF-36 questionnaire.
- The EQ-5D questionnaire.
- Health Resource Use.

A summary table containing descriptive statistics only of subject physical activity will also be presented. The summary tables should be presented by age group.

The following information item is obtained from the eCRF:

- Haemophilia joint health score (*Joint score [HJHS]* eCRF panel).

The following information items are obtained from the ERT third party vendor diary data:

- Haemo-SYM item responses and scores.
- SF-36 item responses and scores.
- EQ-5D item responses and scores.
- Health resource utilization.
- Physical activity records.

7.2.1 Haemophilia Joint Health Score (HJHS) Questionnaire

The HJHS is a questionnaire based assessment of the physical structure and function of the joints in subjects with haemophilia. Each joint is assessed in terms of swelling, muscle atrophy, crepitus on motion, extension, flexion loss, joint pain and joint strength. A global gait score is separately assessed, ranging from '0' (indicating all skills are within normal limits), to '4' (indicating that no skills are within normal limits). The global gait score combined with the joint scores, forms the HJHS total score. A lower HJHS score indicates a better condition of the joint. Therefore, negative change scores indicate that symptoms have improved.

The questions in the HJHS questionnaire are scored as set out in Table 1:

Table 1 HJHS Questionnaire Item Scores

Item	Score
Swelling	No Swelling: 0
	Mild: 1

Item	Score
	Moderate: 2
	Severe: 3
	Non evaluable: No score
Duration (Swelling)	No Swelling or < 6 months: 0
	≥ 6 months: 1
	Non evaluable: No score
Muscle Atrophy	None: 0
	Mild: 1
	Severe: 2
	Non evaluable: No score
Crepitus on Motion	None: 0
	Mild: 1
	Severe: 2
	Non evaluable: No score
Flexion Loss	< 5 degrees: 0
	5 degrees to 10 degrees: 1
	11 degress to 20 degrees: 2
	> 20 degrees: 3
	Non evaluable: No score
Extension Loss	< 5 degrees: 0
	5 degrees to 10 degrees: 1
	11 degress to 20 degrees: 2
	> 20 degrees: 3
	Non evaluable: No score
Joint Pain	No pain through active range of motion: 0
	No pain through active range; only pain on gentle overpressure or palpitation: 1
	Pain through active range: 2
	Non evaluable: No score
Strength	Holds test position against gravity with maximum resistance (gr.5): 0
	Holds test position against gravity with moderate resistance (but breaks with maximum resistance (gr.4): 1
	Holds test position with minimal resistance (gr3.+) or holds test position against gravity (gr.3): 2
	Able to partially complete ROM against gravity (gr.3-/2+), or able to move through ROM gravity eliminated (gr.2-): 3
	Trace (gr.1) or no muscle contraction (gr.0): 4
	Non evaluable: No score
Global Gait Score	All skills are within normal limits: 0
	One skill is not within normal limits: 1
	Two skills are not within normal limits: 2
	Three skills are not within normal limits: 3
	No skills are within normal limits: 4
	Non evaluable: No score

The following derivations will be made based of the eCRF reported results:

- The joint totals (per assessment) are calculated as:

$$Joint\ Totals = \sum Individual\ item\ scores\ per\ joint\ within\ a\ subject$$

- The sum of joint totals (per assessment) is calculated as:

$$Sum\ of\ Joint\ Totals = \sum Joint\ totals\ within\ a\ subject$$

- The HJHS total score is calculated as:

$$HJHS\ Total\ Score = Sum\ of\ Joint\ Totals + Global\ Gait\ Score$$

A Wilcoxon Signed Rank test for paired samples will be used to assess the within treatment arm change in HJHS total score between baseline and completion for any significant statistical differences. The following SAS® code can be used:

```
Proc Univariate Data = <Dataset>;
  Var <Change>;
  By <Treatment>
  ODS Output TestsForLocation = <Outdata>
 (WHERE = (test = 'Signed Rank'));
Run;
Quit;
```

Where <Dataset> refers to the input dataset, <Change> the change from baseline at the completion visit, <Treatment> then assigned treatment arm and <Outdata> the resulting dataset from the procedure containing the inferential statistics for presentation.

A Mann-Whitney U test will be used to assess the between treatment arm change in HJHS total score from baseline to completion for any significant statistical differences. The exact p-value should be selected and presented. The following SAS® code can be used:

```
Proc NPAR1WAY Data = <Dataset> Wilcoxon;
  Class <Treatment>;
  Var <Change>;
  exact Wilcoxon /MC;
```

```
  ODS Output Wilcoxontest = <Outdata>;
Run;
Quit;
```

Where <Dataset> refers to the input dataset, <Treatment> the assigned treatment arm, <Change> the change from baseline at the completion visit and <Outdataset> the resulting dataset from the procedure containing the inferential statistics for presentation.

Statistical significant differences are present if a p-value of <0.05 is obtained.

Values for the Wilcoxon Rank Sum and Mann-Whitney U tests will be selected using the distribution based, ½ standard deviation minimal important difference (MID) threshold as promoted by Norman et al[3]. Change in subject HJHS total score from baseline at the completion visit > ½ SD of the baseline total scores across all subjects should be considered a MID and will be included in both the Wilcoxon Rank sum test as well as the Mann-Whitney U test.

7.2.1.1 X-ray of Impaired Joints

A subject listing for x-rays of impaired joints will be presented using the SAS. No summary table presentation is planned for X-ray results.

The following information item is obtained from the eCRF:

- X-ray of impaired joints (*X-Ray of Impaired Joints* eCRF panels).

7.2.2 Haemophilia Symptom (Haemo-SYM) Questionnaire

The haemophilia symptom questionnaire (Haemo-Sym) is a self reported instrument of measuring symptom severity in patients with haemophilia and has two subscales: pain and bleeds. Lower Haemo-SYM scores indicate fewer symptoms. Therefore, negative change scores indicate that symptoms have improved.

The questions in the Haemo-Sym questionnaire are assigned to the subscales of pain and bleeds as set out in Table 2:

Table 2 Haemo-Sym Questionnaire Subscales

Question (Severity of…)	Subscale
Spontaneous bleeding in my joints (unrelated to injury or activity)	Bleed
Spontaneous bleeding in my muscles (unrelated to injury or activity)	Bleed
Prolonged bleeding after injury in spite of treatment	Bleed

Question (Severity of…)	Subscale
Intense pain because of bleeding event	Bleed
Pain because of swelling in my joints	Pain
Joint pain due to active bleed	Bleed
Bleeding during personal hygiene routine (during shaving, tooth brushing or flossing)	Bleed
Pain because of climbing stairs	Pain
Pain upon waking in the morning	Pain
Constant pain	Pain
Pain because of active arthritis	Pain
Pain in my muscles	Pain
Pain that needs medication	Pain
Joint sensitivity to weather conditions	Pain
Reduced range of joint movement	Pain
Joint deformity	Pain
Sleep disturbance because of pain or bleeds	Pain
Blood in my urine	None
Nose bleeds	None

Results are assigned scores as follows:

- Absent = 0.
- Very mild = 1.
- Mild = 2.
- Moderate = 3.
- Severe = 4.
- Very severe = 5.

The following derivations will be made based of the subject diary reported results:

- The score for each subscale is determined only if at least 50% of the results in that subscale is available. The score should be determined as:

$$Score = \frac{MeanScore}{5} \times 100$$

where MeanScore is the mean of the available results in the particular subscale. If less than 50% of the results in a subscale is available, then no score will be calculated for that subscale.

- The total score for the Haemo-Sym questionnaire should be determined as the mean score of the two subscales should both subscale scores be available.

Within treatment arm change and between treatment arm change in Haemo-SYM total score as well as bleed and pain severity between baseline and completion will be tested for any statistical significant differences in a similar manner as described in Section 7.2.1: Haemophilia Joint Health Score (HJHS) Questionnaire.

Items to be included in these tests as part of the secondary efficacy outcomes are:

- Change in Haemo-SYM total score.

Items to be included in these tests as part of the exploratory efficacy outcomes are:

- Change in bleed severity total score.
- Change in pain severity total score.

7.2.3 Short-Form 36 (SF-36) Questionnaire

The Short-Form 36 (SF-36) is a self-administered, validated questionnaire designed to measure general health related quality of life. The questionnaire is divided in eight domains including: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. From this questionnaire two summary scores can be calculated, the physical component score and the mental component score.

Information on the SF-36 is obtained from electronic patient diaries as supplied by the third party vendor eRT.

The questions in the SF-36 are assigned to domains and scored as set out in Table 3.

Table 3 SF-36 Scoring for Individual Questions

Question	Domain	Score
1. In general, would you say your health is:	General Health (GH)	Excellent: 5 Very Good: 4.4 Good: 3.4 Fair: 2 Poor: 1
2. Compared to one year ago, how would you rate your health in general now?	No Scale	Much better now than one year ago: 1 Somewhat better now than one year ago: 2 About the same as one year ago: 3 Somewhat worse now than one year ago: 4 Much worse now than one year ago: 5
3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?		

Question	Domain	Score
3a. Vigorous activities	Physical Functioning (PF)	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3b. Moderate activities	Physical Functioning (PF)	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3c. Lifting or carrying groceries	Physical Functioning (PF)	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3d. Climbing several flight of stairs	Physical Functioning (PF)	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3e. Climbing one flight of stairs	Physical Functioning (PF)	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3f. Bending, kneeling or stooping	Physical Functioning (PF)	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3g. Walking more than a mile	Physical Functioning (PF)	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3h. Walking several hundred yards	Physical Functioning (PF)	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3i. Walking one hundred yards	Physical Functioning (PF)	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3j. Bathing or dressing yourself	Physical Functioning (PF)	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?		
4a. Cut down on the amount of time you spent on work or other activities	Role-Physical (RP)	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
4b. Accomplished less than you would like	Role-Physical (RP)	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
4c. Were limited in the kind of work or other activities	Role-Physical (RP)	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
4d. Had difficulty performing the work or other activities (for example, it took extra effort)	Role-Physical (RP)	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?		

Question	Domain	Score
5a. Cut down on the amount of time you spent on work or other activities.	Role-Emotional (RE)	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
5b. Accomplished less than you would like	Role-Emotional (RE)	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
5c Did work or other activities less carefully than usual	Role-Emotional (RE)	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?	Social Functioning (SF)	Not at all: 5 Slightly: 4 Moderately: 3 Quite a bit: 2 Extremely: 1
7. How much bodily pain have you had during the past 4 weeks?	Bodily Pain (BP)	None: 6 Very mild: 5.4 Mild: 4.2 Moderate: 3.1 Severe: 2.2 Very severe: 1
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Bodily Pain (BP)	If Question 7 Answered: Not at all (and Question 7 = None): 6 Not at all (and Question 7 not None): 5 A little bit: 4 Moderately: 3 Quite a bit: 2 Extremely: 1 If Question 7 Not Answered: Not at all: 6 A little bit: 4.75 Moderately: 3.5 Quite a bit: 2.25 Extremely: 1
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...		
9a. Did you feel full of life?	Vitality (VT)	All of the time: 5 Most of the time: 4 Some of the time: 3 A little of the time: 2 None of the time: 1
9b. Have you been very nervous?	Mental Health (MH)	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5

Question	Domain	Score
9c. Have you felt so down in the dumps that nothing could cheer you up?	Mental Health (MH)	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
9d. Have you felt calm and peaceful?	Mental Health (MH)	All of the time: 5 Most of the time: 4 Some of the time: 3 A little of the time: 2 None of the time: 1
9e. Did you have a lot of energy?	Vitality (VT)	All of the time: 5 Most of the time: 4 Some of the time: 3 A little of the time: 2 None of the time: 1
9f. Have you felt downhearted and depressed?	Mental Health (MH)	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
9g. Did you feel worn out?	Vitality (VT)	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
9h. Have you been happy?	Mental Health (MH)	All of the time: 5 Most of the time: 4 Some of the time: 3 A little of the time: 2 None of the time: 1
9i. Did you feel tired?	Vitality (VT)	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
10. During the past 4 weeks how much of the time has your physical health or emotional problems interfered with your social activities (like visiting fiends, relatives etc.)?	Social Functioning (SF)	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
11. How true or false is each of the following statements for you?		
11a. I seem to get sick a little easier than other people	General Health (GH)	Definitely true: 1 Mostly true: 2 Don't know: 3 Mostly false: 4 Definitely false: 5
11b. I am as healthy as anybody I know	General Health (GH)	Definitely true: 5 Mostly true: 4 Don't know: 3 Mostly false: 2 Definitely false: 1
11c. I expect my health to get worse	General Health (GH)	Definitely true: 1 Mostly true: 2 Don't know: 3 Mostly false: 4 Definitely false: 5

Question	Domain	Score
11d. My health is excellent	General Health (GH)	Definitely true: 5 Mostly true: 4 Don't know: 3 Mostly false: 2 Definitely false: 1

After scores have been assigned as in Table 3, raw scores for each domain should be calculated as set out in Table 4.

Table 4 SF-36 Scoring for Domains

Domain	Items to Sum	Lowest and Highest Possible Score	Possible Raw Score Range
Physical Functioning (PF)	3a + 3b + 3c + 3d + 3e + 3f + 3g + 3h + 3i + 3j	10, 30	20
Role-Physical (RP)	4a + 4b + 4c + 4d	4, 20	16
Bodily Pain (BP)	7 + 8	2, 12	10
General Health (GH)	1 + 11a + 11b + 11c + 11d	5, 25	20
Vitality (VT)	9a + 9e + 9g + 9i	4, 20	16
Social Functioning (SF)	6 + 10	2, 10	8
Role-Emotional (RE)	5a + 5b + 5c	3, 15	12
Mental Health (MH)	9b + 9c + 9d+ 9f + 9h	5, 25	20

The following derivations will be made based of the subject diary reported results:

- The score for each domain should be transformed to a 0 – 100 range using the following formula:

$$Transf.Domain = \frac{[(Actual\ Raw\ Score - Lowest\ Possible\ Raw\ Score)]}{Possible\ Raw\ Score\ Range} \times 100$$

- A z-score standardization of the SF-36 transformed domain scores should be determined as follows:
  - $PF_z = \frac{PF - 83.29094}{23.75883}$
  - $RP_z = \frac{RP - 82.50964}{25.52028}$
  - $BP_z = \frac{BP - 71.32527}{23.66224}$
  - $GH_z = \frac{GH - 70.84570}{20.97821}$

- $VT_z = \frac{VT - 58.31411}{20.01923}$
- $SF_z = \frac{SF - 84.30250}{22.91921}$
- $RE_z = \frac{RE - 87.39733}{21.43778}$
- $MH_z = \frac{MH - 74.98685}{17.75604}$

- After the z-scores have been determined, the z-scores will be used to determine norm-based scores that will be presented in listings and summaries. The norm based scores should be determined as:

$$XX_N = 50 + (XX_z \times 10)$$

where XX represents the difference domains (PF, RP, BP, GH, VT, SF, RE and MH).

- The raw aggregate summary scores for the physical and mental components are determined as follows:
  - $AGG_{Phys} = (PF_z \times 0.42402) + (RP_z \times 0.35119) + (BP_z \times 0.31754) + (GH_z \times 0.24954) + (VT_z \times 0.02877) + \big(SF_z \times (-0.00753)\big) + \big(RE_z \times (-0.19206)\big) + \big(MH_z \times (-0.22069)\big)$
  - $AGG_{Ment} = \big(PF_z \times (-0.22999)\big) + \big(RP_z \times (-0.12329)\big) + \big(BP_z \times (-0.09731)\big) + \big(GH_z \times (-0.01571)\big) + (VT_z \times 0.23534) + (SF_z \times 0.26876) + (RE_z \times 0.43407) + (MH_z \times 0.48581)$

- The normalized aggregate scores that will be presented in listings and summaries are determined as:

$$YY_N = 50 + (AGG_{YY} \times 10)$$

where YY is either the physical component score or mental component score.

- Any domain with less than half of the questions answered will have no score calculated. For scales with any questions not answered, but with more than half of

the questions answered, the raw scale should be adjusted in terms of the lowest and highest possible score, including the possible raw range. All other scores will be affected by this change in transformed score. As an example, if question 3a is not answered, then the lowest score for physical functioning is to change from 10 to 9, the highest score is to change from 30 to 27 and the possible raw range from 20 to 18. The new values will be used in determining the transformed score for physical functioning.

Within treatment arm change and between treatment arm change in SF-36 total score as well as the physical and mental component scores between baseline and completion will be tested for any statistical significant differences in a similar manner as described in Section 7.2.1: Haemophilia Joint Health Score (HJHS) Questionnaire.

Items to be included in these tests as part of the secondary efficacy outcomes are:

- Change in physical domain component scores.

Items to be included in these tests as part of the exploratory efficacy outcomes are:

- Change in mental domain component scores.

7.2.4 Euro Quality of Life-5 Dimension (EQ-5D) Questionnaire

The EQ-5D questionnaire is a self-administered, standardized instrument for the measurement of health status regards quality of life.

The EQ-5D comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity with a score from 1 to 5 (no problems, slight problems, moderate problems, severe problems, and extreme problems). The severity score on each individual dimension is combined to form a unique EQ-5D health state as a 5-digit code allowing for a total of 3125 health states.

For example, state 11111 indicates no problems on any of the 5 dimensions. These data will be converted into a weighted health state index by applying scores from EQ-5D value sets elicited from general population samples (the base case will be the United Kingdom valuation set, with other country value sets applied as available).

In addition to the descriptive system, subjects also assess their health on the day of assessment on a visual analogue scale (VAS), ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately.

Information on the EQ-5D is obtained from electronic subject diaries as supplied by the third party vendor eRT.

The following derivations will be made based of the subject diary reported results:

- The unique 5-digit health code per subject per assessment which is obtained by concatenating the individual scores of the five domains in their order as presented on the questionnaire itself.

- The utility total score should only be derived and calculated as follows if none of the 5 component scores are missing (depending on the country/region applicable) using both "VAS" value sets and the TTO value sets:

    - For all countries excluding Germany, the utility total score using "VAS" value sets can be derived as:

$$\begin{aligned} Utility\ Total\ Score \\ &= W_{FH} + W_{N2} \times N2 + W_{N3} \times N3 + W\_MO2 \times MO2 \\ &+ W\_MO3 \times MO3 + W\_SC2 \times SC2 + W\_SC3 \times SC3 \\ &+ W\_UA2 \times UA2 + W\_UA3 \times UA3 + W\_PD2 \times PD2 \\ &+ W\_PD3 \times PD3 + W\_AD2 \times AD2 + W\_AD3 \times AD3 \end{aligned}$$

where the variables above are defined below in Table 5 and Table 6:

Table 5 EQ-5D Variable Definitions

Condition	Condition Code (Possible Values: 0 and 1)	Weight Name
Full health (11111)		W_FH
At least one 2 or 3 (N2)	N2	W_N2
At least one 3 (N3)	N3	W_N3
Mobility = 2	MO2	W_MO2
Mobility = 3	MO3	W_MO3
Self Care = 2	SC2	W_SC2
Self Care = 3	SC3	W_SC3
Usual Activities = 2	UA2	W_UA2

Condition	Condition Code (Possible Values: 0 and 1)	Weight Name
Usual Activities = 3	UA3	W_UA3
Pain/Discomfort = 2	PD2	W_PD2
Pain/Discomfort = 3	PD3	W_PD3
Anxiety/Depression = 2	AD2	W_AD2
Anxiety/Depression = 3	AD3	W_AD3

Table 6 EQ-5D VAS Value Sets (Excluding Germany)

Weight Name	Belgium	Denmark	Europe	Finland	New Zealand	Slovenia	Spain	UK
W_FH	1	1	1	1	1	1	1	1
W_N2	-0.152	-0.225	-0.1279	-0.158	-0.2041	-0.128	-0.1502	-0.155
W_N3	-0.256	0	-0.2288	0	-0.2165	0	-0.2119	-0.215
W_MO2	-0.074	-0.126	-0.0659	-0.058	-0.0753	-0.206	-0.0897	-0.071
W_MO3	-0.148	-0.252	-0.1829	-0.230	-0.1506	-0.412	-0.1794	-0.182
W_SC2	-0.083	-0.112	-0.1173	-0.098	-0.0714	-0.093	-0.1012	-0.093
W_SC3	-0.166	-0.224	-0.1559	-0.143	-0.1428	-0.186	-0.2024	-0.145
W_UA2	-0.031	-0.064	-0.0264	-0.047	-0.0136	-0.054	-0.0551	-0.031
W_UA3	-0.062	-0.128	-0.0860	-0.131	-0.0272	-0.108	-0.1102	-0.081
W_PD2	-0.084	-0.078	-0.0930	-0.111	-0.0798	-0.111	-0.0596	-0.084
W_PD3	-0.168	-0.156	-0.1637	-0.153	-0.1596	-0.222	-0.1192	-0.171
W_AD2	-0.103	-0.091	-0.0891	-0.160	-0.0920	-0.093	-0.0512	-0.063
W_AD3	-0.206	-0.182	-0.1290	-0.196	-0.1840	-0.186	-0.1024	-0.124

- For Germany, the utility total score using the "VAS" value set can be derived as:

$$\begin{aligned} &Utility\ Total\ Score \\ &\quad = W\_FH \times W\_N2\text{^}N2 \times W\_MO2\text{^}MO2 \\ &\quad \times W\_MO3\text{^}MO3 \times W\_SC2\text{^}SC2 \times W\_SC3\text{^}SC3 \\ &\quad \times W\_UA2\text{^}UA2 \times W\_UA3\text{^}UA3 \\ &\quad \times W\_PD2\text{^}PD2\ W\_PD3\text{^}PD3 \times W\_AD2\text{^}AD2 \\ &\quad \times W\_AD3\text{^}AD3 \end{aligned}$$

where the variables above are defined in Table 5 and Table 7:

Table 7 EQ-5D Vas Values for Germany

Weight Name	Germany
W_FH	1
W_N2	0.9256
W_MO2	0.9447
W_MO3	0.3927
W_SC2	0.808
W_SC3	0.4702
W_UA2	0.8803
W_UA3	0.5538
W_PD2	0.9745
W_PD3	0.4671
W_AD2	0.8174
W_AD3	0.4682

- For all countries excluding the US, the utility total score using "TTO" value sets can be derived as:

$$\begin{aligned} &Utility\ Total\ Score \\ &\quad = W\_FH + W\_N2 \times N2 + W\_N3 \times N3 + W\_MO2 \times MO2 \\ &\quad + W\_MO3 \times MO3 + W\_SC2 \times SC2 + W\_SC3 \times SC3 \\ &\quad + W\_UA2 \times UA2 + W\_UA3 \times UA3 + W\_PD2 \times PD2 \\ &\quad + W\_PD3 \times PD3 + W\_AD2 \times AD2 + W\_AD3 \times AD3 \end{aligned}$$

where the variables above are defined in Table 5 and Table 8 .

Table 8 EQ-5D TTO Value Sets (Excluding USA)

Weight Name	Denmark	Germany	Japan	Netherlands	Spain	UK	Zimbabwe
W_FH	1	1	1	1	1	1	1
W_N2	-0.114	-0.001	-0.152	-0.071	-0.024	-0.081	-0.100
W_N3	0	-0.323	0	-0.234	-0.291	-0.269	0
W_MO2	-0.053	-0.099	-0.075	-0.036	-0.106	-0.069	-0.056
W_MO3	-0.411	-0.327	-0.418	-0.161	-0.43	-0.314	-0.204
W_SC2	-0.063	-0.087	-0.054	-0.082	-0.134	-0.104	-0.092
W_SC3	-0.192	-0.174	-0.102	-0.152	-0.309	-0.214	-0.231
W_UA2	-0.048	0	-0.044	-0.032	-0.071	-0.036	-0.043
W_UA3	-0.144	0	-0.133	-0.057	-0.195	-0.094	-0.135
W_PD2	-0.062	-0.112	-0.08	-0.086	-0.089	-0.123	-0.067
W_PD3	-0.396	-0.315	-0.194	-0.329	-0.261	-0.386	-0.302
W_AD2	-0.068	0	-0.063	-0.124	-0.062	-0.071	-0.046
W_AD3	-0.367	-0.065	-0.112	-0.325	-0.144	-0.236	-0.173

- For USA, the utility total score using the "TTO" value set can be derived as:

$$Utility\ Total\ Score = W\_FH + W\_MO2 \times MO2 + W\_MO3 \times MO3 + W\_SC2 \times SC2 + W\_SC3 \times SC3 + W\_UA2 \times UA2 + W\_UA3 \times UA3 + W\_PD2 \times PD2 + W\_PD3 \times PD3 + W\_AD2 \times AD2 + W\_AD3 \times AD3 + W\_D1 \times D1 + W\_I2\_SQ \times I2\_SQ + W\_I3 \times I3 + W\_I3\_SQ \times I3\_SQ$$

where the variables above are defined in Table 5, Table 9 and Table 10:

Table 9 EQ-5D USA Additional Variable Definitions

Variable Description	Variable	Possible Values	Weight
Number of movements away from full health beyond the first	D1	0, 1, 2, 3, 4	W_D1 = 0.140
Square if I2 (I2 = Number of dimensions at level 2 beyond the first)	I2_SQ	0, 1, 4, 9, 16	W_I2_SQ = -0.011
Number of dimensions at level 3 beyond the first	I3	0, 1, 2, 3, 4	W_I3 = 0.122
Square if I3	I3_SQ	0, 1, 4, 9, 16	W_I3_SQ = 0.015

Table 10 EQ-5D Vas Values for USA

Weight Name	USA
W_FH	1
W_MO2	-0.146
W_MO3	-0.558
W_SC2	-0.175
W_SC3	-0.471
W_UA2	-0.14
W_UA3	-0.374
W_PD2	-0.173
W_PD3	-0.537
W_AD2	-0.156
W_AD3	-0.45

Within treatment arm change and between treatment arm change in EQ-5D utility total score as well as the VAS score between baseline and completion will be tested for any statistical significant differences in a similar manner as described in Section 7.2.1: Haemophilia Joint Health Score (HJHS) Questionnaire.

The following EQ-5D total scores form part of both the secondary and exploratory efficacy outcomes:

- Utility total score.
- VAS score.

7.2.5 Physical Activity

Information on subject physical activity levels are obtained from electronic patient diaries as supplied by the third party vendor eRT.

Only days with more than 15 minutes of exercise are recorded in the subject diaries as part of the physical activity recording.

The per subject total number of physical activity days should be summarized by level of exercise (mild, moderate or strenuous) by using descriptive statistics.

The change in days of physical activity participation from baseline to completion between the two treatment arms will be assessed by descriptive statistics (point estimates and their 95% CIs) only.

7.2.6 Weigh-adjusted Consumption of BAX 855

Derivations and definitions for weigh-adjusted consumption of BAX 855 is discussed in Section 6.5: Extent of Exposure.

The weight-adjusted consumption fo BAX 855 will be summarized in a table, using descriptive statistics only.

7.2.7 Health Resource Use

The following information is obtained from the subject diaries as provided by the third party vendor eRT.

- Health resource events and usage.

The following derivations will be made based of the subject diary reported results:

- Number of days in hospital should be calculated for a subject by summating all of the individual durations (days), a subject was hospitalized.
- Number of days unable to go to school or work should be calculated by summating the number of days as indicated in the subject diaries.

- Number of days unable to carry out all usual activities should be calculated by summating the number of days as indicated in the subject diaries.

Within treatment arm change and between treatment arm change in Health resource usage between baseline and completion will be tested for any statistical significant differences in a similar manner as described in Section 7.2.1: Haemophilia Joint Health Score (HJHS) Questionnaire.

7.2.8 Surgery

Subject listings will be presented for the following surgery related items using the SGAS:

- Surgical report.
- Preoperative FVIII substitution plan (including modifications).
- Estimated and observed blood loss (including drain removal blood loss).
- Hemostatic efficacy assessments.
- Drain removal.
- Postoperative prophylaxis.
- Transfusion Requirements.

Summary tables containing descriptive statistics will be presented for surgery related blood loss and transfusion requirements using the SAS by age group.

The following information items are obtained from the eCRF:

- Surgical report information (Surgical Report eCRF panel).
- Preoperative FVIII substitution information (Preoperative FVIII Substitution Plan and Modifications of Preoperative FVIII Substitution Plan eCRF panels).
- Surgery related blood loss (Estimated Blood Loss, Surgical Report and Post-Operative 24 Hours/Drain removal Blood loss eCRF panels).
- Postoperative prophylaxis (Postoperative Prophylaxis eCRF panel).
- Transfusion requirements (Transfusion Requirements eCRF panel).

7.3 Sensitivity Analyses

A sensitivity analysis will be performed on the primary outcome measure as described in Section: 7.1.2: Bleeding Episodes.

8. SAFETY EVALUATION

Safety evaluation results form part of the secondary objectives of this study.

8.1 Adverse Events

Subject listings will be presented for all AEs using the SAS with breakdowns by seriousness and occurrence before of after first infusion of BAX 855. Summary tables of AEs that occurred during of after first infusion BAX 855 will be presented using the SAS including breakdowns by relationship to BAX 855, seriousness and severity.

The following information items are obtained from the eCRF:

- Adverse event details per subject (Adverse Events eCRF panel).
- Date and time of BAX 855 administration (Study Infusions eCRF panels).
- Reason for not completing the study (Study Completion/Termination eCRF panel).

Adverse events are coded using the Medical Dictionary for regulatory activities (MedDRA) as documented in the Data Management documentation at the time of performing the analysis.

The following derivations will be made based of the eCRF reported results:

- AEs are considered to have occurred during or after BAX 855 administration if:
  - The known start date and/or time of the AE is equal to or after the date and/or time of first BAX 855 administration in the current study, which is defined for safety analysis purposes as the PK-infusion for dose determination.
  - The eCRF question “When did event occur in relation to treatment with BAX 855 ?” has a response of any of the following:
    - During PK infusion.
    - Within 24 hours after PK infusion.
    - After more than 24 hours from PK infusion.
    - Before first treatment with BAX 855.
    - During BAX 855 treatment.
    - Within 24 hours after last BAX 855 treatment.
    - After more than 24 hours from last BAX 855 treatment.

- Time since last BAX 855 infusion should be determined as:

$$Time = [Start\ Date/Time\ of\ AE] - [Date/Time\ of\ Last\ BAX\ 855\ Infusion]$$

where the date/time of last BAX 855 exposure is the last possible BAX 855 administration, regardless of reason, prior to the start of the AE. Time since last BAX 855 infusion should only be determined if the full start date (regardless of whether time is known or not) of the AE is known. Time since last BAX 855 infusion will be presented in either hours or days, based on the following criteria:

  - Presented in hours if start time of AE is known and time since last BAX 855 infusion is < 24 hours.
  - Presented in days if start time of AE is known and time since last BAX 855 infusion is ≥ 24 hours.
  - Presented in days if start time of AE is not known.

- Duration of AE should be determined as:

$$Duration = [End\ Date/Time\ of\ AE] - [Start\ Date/Time\ of\ AE]$$

The duration of an AE will be presented in either hours or days, based on the following criteria:

  - Presented in hours if both start time and end time of the AE is known and the duration is < 24 hours.
  - Presented in days if both start time and end time of the AE is known and the duration is ≥ 24 hours.
  - Presented in days if either start time or end time or both are unknown.
- An AE is considered non-serious if the eCRF question “Was AE serious?” is answered “No” and considered serious if the question is answered “Yes”.
- An AE is considered severe if the eCRF question “Severity” is answered “Severe”.
- An AE is considered related as assessed by the Investigator if the AE is indicated as “Possibly related” or “Probably related” in the eCRF. An AE is considered unrelated as assessed by the Investigator if the AE is indicated as “Not related” or “Unlikely related” in the eCRF.
- An AE is considered related as assessed by the Sponsor if the Sponsor Medic deem the AE related to the study medication. Prior to the execution of any

analyses described in this SAP, a list of all AEs in the database will be provided to the Sponsor Medic to assess relationship from a Sponsor perspective of AE to study medication.

- An AE is considered leading to discontinuation of study medication if action taken in BAX 855 is indicated as "Drug withdrawn" in the eCRF.
- An AE is considered leading to discontinuation of study if the AE is indicated as the primary reason why the subject did not complete the study from the Study Completion/Termination eCRF panel.
- An AE is considered as leading to death if the AE outcome is indicated as "Fatal" in the eCRF.
- An AE will be considered an allergic reaction if the question "Was this event considered to be an allergic reaction to Bax 855" is indicated as "Yes".
- An AE will be considered a thrombotic event if the question "Is this a thrombotic event" is indicated as "Yes" in the eCRF.

Tables should be presented by age group, system organ class (SOC) and PT, the number of subjects who experienced an AE at least once, and the rate of subjects with AE(s).

8.2 Clinical Laboratory Evaluations

Subject listings will be presented on laboratory data from the following sources using the SAS which would include breakdowns for clinically significant values:

- Central laboratory.
- Central laboratory from previous BAX 855 study.
- Local laboratory.

Summary and shift tables will be presented using the SAS for central laboratory asessments broken down by laboratory department:

- Haematology.
- Clinical chemistry.
- Lipids.
- Viral serology.

Box-plots containing descriptive statistics of central laboratory assessments will be presented using the SAS for the following laboratory departments by by age group and treatment arm across visits:

- Haematology.
- Clinical chemistry.
- Lipids.

All laboratory summary tables should be presented by age group and alphabetic assessment name.

Results from the central laboratory will be included in the reporting for this study. Results will be presented using CDISC compliant terms and standard international (SI) units.

The following table provides a list of the different laboratory assessments and their respective departments that are expected to be received from the central laboratory:

Table 11 List of Laboratory Assessments

Department	Assessment Name	Standardized International (SI) Unit
Chemistry	Alanine Aminotransferase (ALT)	U/L
	Aspatate Aminotranferase (AST)	U/L
	Albumin	g/L
	Alkaline Phosphatase	U/L
	Blood Urea Nitrogen (BUN)/Urea	mmol/L
	Bicarbonate	mmol/L
	Chloride	mmol/L
	Creatinine	umol/L
	Glucose	mmol/L
	Potassium	mmol/L
	Sodium	mmol/L
	Total Bilirubin	umol/L
	Total Protein	g/L
Coagulation	activated Prothrombin Time (aPTT)	sec
	von Willebrand Factor Antigen (vWFA)	%vWF:Ag
HCV Quantitative PCR	Hepatittus C (HCV) Ribonucleic Acid (RNA) Quantitative Polymerase Chain Reaction (PCR)	IU/mL
Haematology	Anisocytosis	
	Basophils/Leukocytes	%
	Basophils	x10E9/L
	Elliptocytes	
	Eosinophils/Leukocytes	%
	Eosinophils	x10E9/L
	Haematocrit	L/L
	Haemoglobin	g/L
	Hypochromasia	
	Large Platelet	
	Lymphocytes/Leukocytes	%
	Lymphocytes	x10E9/L
	Ery. Mean Corposcular Haemoglobin Concentration (MCHC)	g/L
	Ery. Mean Corpuscular Volume (MCV)	fL

Department	Assessment Name	Standardized International (SI) Unit
	Macrocytosis	
	Microcytosis	
	Monocytes/Leukocytes	%
	Monocytes	x10E9/L
	Neutrophils/Leukocytes	%
	Neutrophils	x10E9/L
	Platelet Count	x10E9/L
	Red Bloodcell Count (RBC)	x10E12/L
	Target Cells	
	White Bloodcell Count (WBC)	x10E9/L
Lipids	Cholesterol	mmol/L
	High-density Lipoprotein (HDL) Cholesterol	mmol/L
	Low-density Lipoprotein (LDL)-C	mmol/L
	LDL Cholesterol	mmol/L
	Triglycerides	mmol/L
	Very Low Density Lipoprotein (VLDL) Cholesterol	mmol/L
	VLDL-C (direct LDL)	mmol/L
Genetics	HLA-DQB1 Allele 1	
	HLA-DQB1 Allele 2	
	HLA-DRB1 Allele 1	
	HLA-DRB1 Allele 2	
TBNK Assay	CD3+CD4+ Percentage	%
	CD3+CD4+ Absolute	Cells/uL
Viral Serology	Hepatitis B Surface Antigen (HBsAG)	
	HIV ½ Antibody	
	Hepatitis B Antibodies (Anti-HBs)	
	Hepatitits C Virus Antibodies (Anti-HCV)	
	Anti-HIV ½	
	Total Hepatitis B Virus Core Antibodies (Anti-HBc)	
Note: Laboratory assessments with no entry in the SI unit column do not have a quantitative unit and would have results such as "+1" or trace for example.		

8.2.1 Safety Laboratory Assessments

The following information items are obtained from the eCRF:

- Information from the Investigator on abnormal results is obtained from the eCRF (Central Laboratory eCRF panels).
- Local laboratory testing information (Local Laboratory eCRF panels).

The following derivations will be made based of the eCRF reported results:

- A result will be considered out of range if the observed result is less than the lower limit of the normal range (indicated as "L") or larger than the upper limit of the normal range (indicated as "H"). The normal range is provided by the central laboratory.

- A result is considered clinically significant if indicated as such by the Investigator on the eCRF.
- Quantitative laboratory measurements reported as "< X", i.e., below limit of quantification (BLQ), or "> X", i.e., above limit of quantification (ALQ) should be presented in listings as "< X" or "> X" and summarized in summaries as "X".

8.2.2 Viral Serology

See Table 11 for the viral serology assements to be performed by the central laboratory. This information should be summarized with descriptive statistics (n[%]) only.

8.3 Inhibitor/Antibody Development (Immunogenicity)

Subject listings will be presented for the following items using the ENR:

- Total binding antibodies to FVIII, PEG and CHO protein.
- Inhibitory antibodies to FVIII.
- Subjects included in the immunogenicity analysis for inhibitory antibodies.

Summary tables will be presented for immunogeniticy SAS by age group.

Results on inhibitory antibodies to FVIII and binding antibodies to FVIII, PEG-FVIII and PEG (both Immunoglobulin G [IgG] and immunoglobulin M [IgM]) and anti-CHO antibodies are obtained from the central laboratory.

A subject will be considered to have developed inhibitory antibodies to FVIII if the following criteria are all met:

- Result obtained from the central laboratory are ≥ 0.6 BU.
- Inhibitor is documented at 2 separate timepoints winthin a 2- to 4-week period at the central laboratory.

The following derivations will be made based of the central laboratory results:

- A low titer (responder) inhibitor is defined as ≥ 0.6 BU but ≤ 5 BU.
- A high titer (responder) inhibitor is defined as > 5 BU.

For the purpose of analyses, positive will be considered a worse result than a negative result.

The proportion of subjects who developed inhibitory antibodies to FVIII at any time during the study will be reported, together with exact Clopper-Pearson 95% CIs for the proportion. The subset of subjects included in this analysis are the subjects that developed inhibitory antibodies to FVIII at any time during the study, and any subject that did not develop any inhibitory antibodies to FVIII but had a FVIII inhibitory antibody test result from the central laboratory.

The following SAS® code can be used in the Clopper-Pearson analysis:

```
PROC FREQ Data = <Dataset>;
  Weight <Count>;
  Tables <Result> / BINOMIAL (EXACT CP) ALPHA = 0.05 CL;
RUN;
QUIT;
```

where <Dataset> refers to the input dataset, <Count> the number of subjects with particular result and <Result> the actual result (for example “Yes” or “No”).

8.4 Vital Signs

Subject listings will be presented for vital signs including a breakdown for abnormal vital signs using the SAS. A summary table and shift table will be presented for vital signs using the SAS by age group and alphabetic parameter.

The following information items are obtained from the eCRF:

- Vital signs (Vital Signs eCRF panels) for parameters:
  - Body temperature (°C).
  - Diastolic blood pressure (mmHg).
  - Pulse rate (beats/minute)
  - Respiratory rate (breaths/minute).
  - Systolic blood pressure (mmHg).
  - Weight (kg).

The following derivations will be made based of the eCRF reported results:

- A result will be considered out of range if the observed result is less than the lower limit of the normal range (indicated as "L") or larger than the upper limit of the normal range (indicated as "H"). The normal ranges to be used are:

Table 12 Vital Signs Parameter Ranges

Parameter	Age Range (Years)	
	≥13	≥6 to <12
Respiratory rate (breaths/minute)	5 to 16	14 to 22
Pulse rate (beats/minute)	55 to 100	60 to 95
Systolic blood pressure (mmHg)	90 to 140	100 to 120
Diastolic blood pressure (mmHg)	50 to 89	60 to 75
Body temperature (Celcius)	35 to 37.9	35 to 37.9

- Identification of clinically significant vital signs for inclusion in the vital signs presentations, will be obtained from the Shire medical team following their review of the AE and vital signs data.

8.5 Physical Examination

A subject listing will be presented for physical examinations performed using the SAS. No summary tables are planned to be presented for physical examinations.

The following information item is obtained from the eCRF:

- Physical examination (*Physical Examination* eCRF panel).

9. EVALUATION OF PHARMACOKINETICS

TGA data as well as FVIII activity data and PK parameters for FVIII activity data measured by one-stage clotting and chromogenic assay are provided.

Subject listings for the following items will be presented using the analysis set indicated in brackets:

- Plasma PK sample collection times (SAS).
- Plasma FVIII activity, FVIII antigen and von Willebrand factor antigen (SAS).
- Incremental Recovery (SAS).

- TGA (SAS).
- Pre-infusion-corrected FVIII activity plasma PK parameters by assay (PKAS).
- FVIII activity lambda_z related parameters by assay (PKAS).
- Data excluded from the PK analysis (SAS).
- Data changes observed between original data for dose calculation and final data after database lock as well as the effect on dose recommendation.

Summary tables will be presented for the following items using the PKAS:

- Descriptive statistics on:
  - Observed plasma FVIII activity [IU/dL] by assay.
  - Pre-infusion-adjusted plasma FVIII activity [IU/dL] by assay.
  - Observed TGA parameters (lag time [min], time to peak [min], ETP [nM*min], peak [nM]).
  - Incremental recovery [IU/dL] at 15-30 minutes post-infusion by assay.
  - Calculated plasma FVIII activity trough levels [IU/dL] by scheduled visit and assay.
  - Observed plasma FVIII activity trough levels [IU/dL] within 2 hours of planned infusion interval by scheduled visit and assay.
  - von Willebrand factor antigen.
  - Pre-infusion-corrected PK parameters by assay.
- Correlation and regression of pre-infusion von Willebrand factor antigen and BAX 855 PK parameters by assay.

PK figures will be presented for the following items using the PKAS:

- Arithmetic Mean (±SD) pre-infusion-corrected plasma FVIII activity-time profiles on both linear and semi-logarithmic scales of the PK assessment by assay (both initial and Month 9).
- Box-plots of incremental recovery over time for each treatment arm by assay.
- Box-plots of calculated plasma FVIII activity (IU/dL) trough levels over time by treatment arm and assay.
- Box-plots of observed plasma FVIII activity (IU/dL) trough levels collected within 2 hours of the planned infusion interval over time by the treatment arm and assay.
- Scatter-Plots of the following items versus vWF antigen:
  - BAX 855 $t_{1/2}$.

- Pre-infusion BAX 855 $AUC_{0-\infty}$.
- Pre-infusion BAX 855 AUC_{0-last}.
- Pre-infusion BAX 855 MRT.
- Pre-infusion BAX 855 CL.
- Pre-infusion BAX 855 V_{ss}.
- Pre-infusion BAX 855 C_{max}.

- Individual observed Plasma FVIII activity-time profiles on both linear and semi-logarithmic scales.

9.1 FVIII Activity and TGA Data

For PK assessment visits prior to randomization and steady state after the Month 9 visit (if applicable), observed and pre-infusion-corrected plasma FVIII activity levels, as well as TGA data, at each scheduled collection time point will be summarized using n, mean, SD, CV% minimum, median, maximum, geometric mean and geometric CV%. FVIII activity values or TGA data that are BLQ will be treated as zero for the computation of descriptive statistics. Missing data will be treated as missing. If a concentration/FVIII activity is above the assay quantitation limit (ALQ), the concentration will be set to the upper limit of quantitation (ULOQ), with the upper limit of quantitation defined in the document/CSR. The value will be clearly identified as ULOQ and will be included in all analyses and calculations of descriptive statistics.

Samples with significant deviations from the planned time, as determined by the clinical pharmacokineticist, may be excluded from calculation of descriptive statistics.

If any FVIII activity or TGA data are considered to be spurious (eg, lack of biological plausibility), the reason for exclusion and the analysis (i.e. PK parameter calculation; descriptive statistics) from which the data point was excluded will be documented in a listing.

For pre-infusion-corrected data, all post-infusion FVIII activity values will be corrected for pre-infusion FVIII activity using the method described by Björkman et al[8] as:

$$C_{corrected,t} = \left(1 - \frac{C_{measured,pre-infusion}}{C_{measured,tmax}}\right) \cdot C_{measured,t}$$

where $C_{corrected,t}$ is the resulting adjusted concentration to be used in PK calculations at time t, $C_{measured,pre-infusion}$ is the pre dose concentration, $C_{measured,tmax}$ is the maximum concentration measured post dose, and $C_{measured,t}$ is the measured concentration at time t.

Following pre-infusion-correction, the pre-infusion value is set to zero.

Handling of post-dose FVIII activity values that are BLQ for PK parameter analysis are described in Section 9.2: Pharmacokinetic Parameters

For PK assessment visits at the initial assessment (prior to randomization) and at steady state after the Month 9 visit (if applicable), plots of observed and pre-infusion-corrected arithmetic mean FVIII activity-time data (±SD, as appropriate) will be presented by assay type (one-stage clotting and chromogenic assay) on linear and semi-logarithmic scales. Individual subject observed FVIII activity-time data will be graphically presented on linear and semi-logarithmic scales with both FVIII assays presented on the same plot.

9.2 Pharmacokinetic Parameters

The PK analysis is performed at IQVIA, Overland Park, Kansas, US. IQVIA Standard Operating Procedures and Work Instructions are used as the default methodology, unless otherwise specified.

Subjects with partial data are evaluated on a case-by-case basis to determine if sufficient data is available for reliable estimation of specific PK parameters. For the initial PK assessment, subjects should have followed the protocol-specified washout period of 72-96 hours for the PK assessments to be performed.

The non-compartmental PK parameter calculations are performed on pre-infusion-corrected FVIII activities using the IV infusion model (Model 202) and linear-up/log-down trapezoidal rule within Phoenix® WinNonlin®. All PK analyses are to use the actual sampling times, not nominal times and actual infusion durations. Actual sampling times are defined as time from the start of infusion to the blood sampling collection time. A deviation from the protocol-specified drawing time window is not a reason to exclude an observation from PK parameter calculation. However, samples with unknown collection time and/or where the activity could not be determined are eliminated from the calculations. If the actual doses on a IU/kg basis is outside of the protocol-specified dose of 60 ±5 IU/kg, when calculated dose is rounded to zero decimal places, any parameters calculated for this dose will listed but not included in descriptive statistics.

To ensure that FVIII present prior to the dose (pre-infusion) is not attributed to the calculation of PK parameters, all post-infusion FVIII activity values will be corrected using the method described by Björkman et al[6] as described in Section 9.1: FVIII

Activity and TGA Data. For PK parameter calculation, pre-infusion samples that are BLQ will be assigned a numerical value of zero. Handling of missing pre-infusion values for PK parameter analysis will be decided on a case-by-case basis and the decision will be documented in the Clinical Study Report (CSR).

In addition to post-infusion samples, the lower limit of quantitation (LLOQ) will likewise be adjusted for calculation of PK parameters:

$$LLOQ_{adjusted} = \left(1 - \frac{C_{measured,pre-infusion}}{C_{measured,tmax}}\right) \cdot LLOQ$$

Handling of post-dose values that are below the limit of quantification (BLQ)

For post-infusion FVIII activities that are below the limit of quantitation (BLQ) the following analysis will be performed to assess whether an adjusted value has to be used for calculation of PK parameters. If more than one consecutive value is BLQ, only the first value will be considered for adjustment:

1. Determine the highest adjusted R^2 of the terminal phase using the natural log-transformation of the observed concentration values ($C_{corrected,t}$; omitting BLQ values) as described in Section on "Determination of slope and intercept of the terminal phase".

2. Using the slope and intercept of this best fit, determine the predicted concentration value at the time of the BLQ observation.

3. If the predicted value is below the $LLOQ_{adjusted}$, the determined slope and intercept is the solution. If the predicted value is above the $LLOQ_{adjusted}$, step 1 is repeated using all observed numeric data point and the value of $LLOQ_{adjusted}$ at the time of the BLQ value to calculate slope and intercept of the terminal phase. This solution will be used for calculation of PK parameters.

Determination of slope and intercept of the terminal phase

The slope and intercept of the terminal phase using a natural log-transformation of the concentration values of the terminal phase will be determined (using y=mx+b). The

number of time points to be included for estimation of the terminal phase (intercept and slope) in Phoenix WinNonLin will be determined applying the following rules:

1. Include the last three data points and calculate the slope and the adjusted R^2 for this step; disregard if slope is ≥ 0.

2. Increase the number of last points to include by 1 (i.e. the last 4, 5, 6 datapoints) and calculate the slope and adjusted R^2 up to and including C_{max}; disregard if slope is ≥ 0. The solution is the found for the terminal phase with the highest adjusted R^2.

The following PK parameters will be calculated, if appropriate, for preinfusion-corrected FVIII activity obtained using the one-stage clotting and the chromogenic assays:

Table 12 Calculated PK Parameters

Parameter	Description
$AUC_{0-\infty}$ (IU*h/dL)	Area under the FVIII activity-time curve from zero extrapolated to infinity, calculated by linear-up/log-down trapezoidal method and extrapolated to infinity, calculated as $AUC_{0-last} + C_{last}/\lambda z$, where C_{last} is the estimated concentration at the last quantifiable time point.
AUC_{0-last} (IU*h/dL)	Area under the FVIII activity-time curve from zero to the last quantifiable FVIII activity.
$t_{1/2}$ (h)	Terminal elimination phase half-life, calculated by (ln 2)/λz.
MRT (h)	Mean residence time, calculated as $(AUMC_{0-\infty}/AUC_{0-\infty})$ - TI/2, where TI is the time duration of infusion; calculated only for PK assessment prior to randomization.
CL (dL/kg*h)	Systemic body clearance of drug from plasma, calculated by Dose (IU/kg)/$AUC_{0-\infty}$.
V_{ss} (dL/kg)	Volume of distribution at steady state, calculated by MRT*CL; calculated only for the initial PK assessment (prior to randomization).
C_{max} (IU/dL)	Maximum observed FVIII activity, obtained directly from FVIII activity versus time data.
T_{max} (h)	Time of maximum FVIII activity, obtained directly from FVIII activity versus time data.

In addition, the IR at C_{max} for PK assessments is calculated as:

$$IR\ at\ C_{max} = \frac{C_{max} - C_{pre-infusion}}{Dose\ (\frac{IU}{kg})}$$

where kg refers to the body weight at the time of dosing and C_{max} is the observed maximum concentration prior to correction for pre-infusion values.

The following PK parameters are calculated for diagnostic purposes, where applicable, and listed but will not be summarized:

- λ_z: Apparent terminal rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve. Visual assessment will

be used to identify the terminal linear phase of the concentration-time profile. A minimum of three data points will be used for determination.

- $t_{1/2}$, Interval: The time interval of the log-linear regression used to determine λ_z.Visual assessment is used to identify the terminal phase of the FVIII activity-time profile. A minimum of three data points are used for determination of the terminal phase.
- $t_{1/2}$, N: Number of data points included in the log-linear regression analysis to determine λ_z.
- $R_{sq\_adjusted}$: Goodness-of-fit statistic for calculation of λ_z (coefficient of determination).
- $\%_{AUCex}$: Percentage of $AUC_{0-\infty}$ obtained by extrapolation.

Pharmacokinetic parameters at the initial PK asessment (prior to randomization) and at steady state (after the Month 9 visit; if applicable) will be summarized using descriptive statistics by assay type. Descriptive statistics for PK parameters are to include n, mean, SD, CV%, geometric mean, geometric CV%, minimum, median, and maximum, except that T_{max} should be reported with n, minimum, median, and maximum only.

In this study, individualized doses for the PK-guided dosing were calculated prior to randomization based on the terminal phase/$t_{1/2}$ and IR of the initial PK assessment. During the study conduct, data changes that potentially affect the recommended dose and/or trough level assessments have been noted for some of the subjects in this study. Differences in PK parameters ($t_{1/2}$, IR) and the effect on dose recommendation and trough level calculations were assessed during study conduct and the effect on dose recommendation and trough level assessment was assessed. It was determined that the observed PK data changes have minimal impact on data integrity and that there is no material effect on medical and safety data of patients. Following database lock, differences in PK parameters ($t_{1/2}$, IR) between the initial and final analysis and the effect on dose recommendation and trough level calculations will be assessed again and subjects/data with changes will be presented in listings.

Incremental recovery at 15-30 minutes post infusion over time and FVIII activity trough levels after randomization will be summarized by treatment arm, assay, and scheduled visit using n, mean, SD, CV% minimum, median, maximum, geometric mean, geometric CV%, 1st quartile and 3rd quartile (Q1 and Q3, respectively), and IQR. Incremental recovery and FVIII activity trough levels will be displayed as boxplots by scheduled visit for the two treatment arms.

Box-plots for trough levels for each visit will be presented by assay. As the observed trough levels cannot necessarily be considered trough levels (e.g. due to deviation in sampling time from the individual planned interval), two analysis will be performed:

- For the primary analysis, trough levels will be calculated exactly to the end of the subjects' planned infusion interval using:

$$C_{trough,corrected} = C_{trough,measured} * 2^{(\frac{TAD-Interval}{t_{\frac{1}{2}}})}$$

  where $C_{trough,corrected}$ is the calculated FVIII trough level at the end of the planned interval, $C_{trough,measured}$ is the observed FVIII activity, TAD is the time after the last infusion, and Interval is the individuals' planned interval. For a subject with a T hour infusion interval, trough samples that were collected outside of ±16 hours (the reported half-life of BAX855) of the planned infusion interval, will be excluded from descriptive statistics and graphical representation.

- A secondary analysis will be performed using observed trough samples that are collected within a ±2 hour of the planned interval (e.g., for a subject with T hour infusion interval, no infusion was given in the T-2 hours before the blood draw and there was exactly 1 infusion in the interval T+2 to T-2 before the blood draw; as an example, for a subject with a 48 hour infusion interval, no infusion has been given 46 hours before the blood draw and exactly one infusion has been observed between 50 to 46 hours before the blood draw).

Correlation of pre-infusion VWF:Ag and BAX 855 PK parameters $t_{1/2}$, MRT, $AUC_{0-\infty}$, AUC_{0-last}, CL, V_{ss}, and C_{max} of the initial and Month 9 PK assessment will be assessed by scatterplots and Spearman rank correlation coefficient.

Correlation testing between the average of various coagulation parameters (TGA parameters and FVIII trough levels) and ABR are discussed in Section 7.1.2: Bleeding Episodes.

10. EVALUATION OF QUALITY OF LIFE

The following quality of life measurement instruments utilized in this study are discussed in Section 7.2: Analysis of Secondary Efficacy Outcome Measures:

- HJHS questionnaire.

- Haemo-SYM questionnaire.
- SF-36 questionnaire.
- EQ-5D questionnaire.
- Subject physical activity level.

The following quality of life measurement instrument utilized in this study is discussed in Section 7.2.7: Health Resource Use:

- Health Resource utilization.

11. EXPLORATORY ANALYSES

The following exploratory efficacy outcome measures are discussed in Section 7.1.2: Bleeding Episodes:

- Testing for presence of correlations between various coagulation paramters and ABR.

The following exploratory efficacy outcome measures are discussed in Section 7.2: Analysis of Secondary Efficacy Outcome Measures:

- Haemo-SYM questionnaire bleed and pain severity.
- EQ-5D questionnaire.
- SF-36 questionnaire Mental domain and component scores.
- Health resource utilization.

12. ANALYSIS SOFTWARE

All data processing, summarization, and analyses are to utilize SAS® software package, Version 9.4. The noncompartmental PK parameter calculations are to be performed within Phoenix® WinNonlin® 6.4. The software versions used for the analyses will be documented in the CSR. If the use of other software is warranted, the final CSR is to detail what software was used and also the versions actually used.

13. REFERENCES

1) 261303 Protocol, final version incorporating Amendment 1, 2, 3, 4 and 5, 2016OCT18.

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3) Interpretation of Changes in Health-related Quality of Life: The Remarkable Universality of Half a Standard Deviation, Geoffrey R. Norman et al, Medical Care Vol 41, Number 5: 582-592 (2003).

4) Multiple Imputation for Missing Data: Concepts and New Development, Yang C. Yuan, http://www.ats.ucla.edu/stat/sas/library/multipleimputation.pdf

5) Missing Data Sensitivity Analysis for Recurrent Event Data Using Controlled Imputation, Oliver N. Keene et al, Pharmaceutical Statistics Issue 13: 258-264 (2014).

6) Population pharmacokinetics of recombinant factor VIII: the relationships of pharmacokinetics to age and body weight, Björkman S et al, Blood; 119(2): 612-618 (2012).

14. REVISION HISTORY

Version	Version Date	Summary of Changes
1.0		New Document
2.0	31JUL2018	Finalized outstanding PK handling conventions. Added the multiple imputation details of implementation. Added discussion on the inclusion of post-PROPEL data in to the analysis as per protocol. Minor adjustments to text resulting from Sponsor comments on the TLFs.
3.0	19SEP2018	Added text to Section 5.8 Changes to the planned analysis in the protocol to include additional table and listing of 3 000Iu vial resultant IR. Given the removal of duplicate infusions (ex. Same infusion recorded as prophylaxis and as IR infusion and only IR infusionrecord kept), clarified the calculation of OPE in section 5.1.4 Observation period of efficacy.