STATISTICAL ANALYSIS PLAN

BAX 855

A Phase 3b Continuation Study of the Safety and Efficacy of PEGylated Recombinant Factor VIII (PEG-rFVIII; BAX 855) in Prophylaxis of Bleeding in Previously Treated Patients with Severe Hemophilia A

PROTOCOL IDENTIFIER: 261302

Study Sponsor(s): **Baxalta US Inc.**
One Baxter Way
Westlake Village, CA 91362

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna, AUSTRIA

Author: PPD, IQVIA

Protocol: Amendment 8: 2015 MAR 20 (Russia)
Amendment 7: 2015 MAR 20 (Global)

SAP Version #: 3.0

SAP Date: 2018 APR 18

Status: Final

TABLE OF CONTENTS

1. INTRODUCTION AND OBJECTIVES 5

1.1 Study Objectives 5
1.1.1 Primary Objectives 5
1.1.2 Secondary Objectives 5
1.1.2.1 Efficacy 5
1.1.2.2 Safety 6
1.1.3 Exploratory Objectives 6

2. STUDY DESIGN 6

2.1 Inclusion Criteria 7
2.2 Exclusion Criteria 7
2.3 Sample Size and Power Calculations 7
2.4 Randomization and Blinding 7
2.5 Study Stopping Rules 7
2.6 Study Assessments 7
2.7 Data Monitoring Committee 7

3. STUDY OUTCOME MEASURES 7

3.1.1 Primary Outcome Measures 7
3.1.1.1 Safety 7
3.1.1.2 Efficacy 8
3.1.2 Secondary Outcome Measures 8
3.1.2.1 Efficacy 8
3.1.2.2 Safety 8
3.1.2.3 Patient Reported Outcomes 8
3.1.3 Exploratory Outcomes Measure 9

4. ANALYSIS SETS 9

4.1 All Subjects Enrolled Set (ENR) 9
4.2 Safety Analysis Set (SAS) 9
4.3 Full Analysis Set (FAS) 9
4.4 Per Protocol Analysis Set (PPAS) 10
4.5 Pharmacokinetic Analysis Set (PKAS) 10

5. STATISTICAL CONSIDERATIONS 11

5.1 Interim Analyses 11
5.2 Final Analysis 11
5.3 Reference Start Date and Study Day 11
5.4 Handling of Missing, Unused, and Spurious Data 12
5.5 Definition of Baseline 13
5.6 Definition of Visit Windows 13
5.7 Changes from the Planned Statistical Analysis in Protocol 13
5.8 Statistical Tests 13
5.9 Common Calculations 15
5.10 Multicenter Studies 15
5.11 Examination of Subgroups 15
5.12 Multiple Comparisons/Multiplicity 16

6. STUDY SUBJECTS 16

6.1 Disposition of Subjects 16
6.2 Demographic and Baseline Characteristics 17
6.3 Medical History 19
6.4 Hemophilia A Treatment History 19
6.5 Prior PEGylated Medication History 19
6.6 Prior and Concomitant Medications and Non-drug Therapies 20
6.7 Extent of Exposure 20
6.8 Measurements of Treatment Compliance 22
6.9 Protocol Deviations 23

7. EFFICACY EVALUATION 24

7.1 Bleeding Episodes 24
7.2 Weight-adjusted Consumption of BAX 855 28

8. SAFETY EVALUATION 28

8.1 Adverse Events 28
8.2 Clinical Laboratory Evaluations 31
8.3 Inhibitor/Antibody Development 32
8.4 Vital Signs 33
8.5 Physical Examination 34
8.6 Comments 34

9. EVALUATION OF PATIENT REPORTED OUTCOMES 34

9.1 Haemophilia Symptom Questionnaire (Haemo-Sym) 34
9.2 Short-Form 36 (SF-36) Questionnaire 36
9.3 Pediatrics Quality of Life Questionnaire (PedsQL) 42

10. EVALUATION OF EXPLORATORY OUTCOME MEASURES 45

10.1 Patient Satisfaction Questionnaire 45
10.2 Patient Activity Level 45
10.3 Hospitalizations Due to Hemophilia A 45
10.4 Health Resource Use Other Than Hospitalizations.....45
10.5 TGA Parameters, FVIII Trough Levels, Incremental Recovery and Comparisons against ABR 46

11. ANALYSIS SOFTWARE 46

12. REVISION HISTORY 47

1. INTRODUCTION AND OBJECTIVES

This document describes the rules and conventions to be used in the planned presentation and analysis of efficacy and safety data for Protocol 261302 as set out in the latest version of the Output Templates. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

The purpose of this study is to continue the evaluation of the safety and efficacy of BAX 855 for prophylaxis and treatment of bleeding episodes in adult and pediatric previously treated patients (PTPs) aged ≤ 75 years with severe hemophilia A. In the Russian Federation, safety and efficacy are only to be assessed in adults aged ≥ 18 and < 75 years at the time of enrollment.

1.1 Study Objectives

1.1.1 Primary Objectives

The co-primary objectives of the study are:

1. To determine the safety of BAX 855 based on the incidence of factor VIII (FVIII) inhibitory antibody development.

2. To determine the efficacy of BAX 855 based on annualized bleeding rate (ABR) of spontaneous bleeding episodes.

1.1.2 Secondary Objectives

1.1.2.1 Efficacy

1. To determine the total ABR (spontaneous and traumatic bleeding episodes).

2. To determine the overall hemostatic efficacy rating of BAX 855 for treatment of breakthrough bleeding episodes.

3. To determine the length of intervals between bleeding episodes.

4. To characterize the hemostatic efficacy of BAX 855 for treatment of bleeding episodes by number of BAX 855 infusions for treatment.

5. To determine total weight-adjusted consumption of BAX 855 for prophylaxis and for treatment of bleeding episodes.

6. To assess Patient Reported Outcomes (PROs) over time for subjects receiving BAX 855.

1.1.2.2 Safety

1. To determine the safety of BAX 855, as assessed by the occurrence of adverse events (AEs) and changes in vital signs and clinical laboratory parameters.

2. To determine the immunogenicity of BAX 855.

1.1.3 Exploratory Objectives

1. To assess patient satisfaction, patient activity levels, and health resource use over time for subjects receiving BAX 855.

2. To determine the potential correlation between thrombin generation assay (TGA) parameters, FVIII trough levels and ABR.

2. STUDY DESIGN

This is a phase 3b, prospective, open label, multi-center study to evaluate the safety and efficacy of BAX 855 for prophylactic use and the control of bleeding episodes in approximately 200 pediatric and adult PTPs ≤ 75 years of age with severe hemophilia A. In the Russian Federation, safety and efficacy are only to be assessed in adults aged ≥ 18 and < 75 years at the time of enrollment. The study plans to include subjects from other BAX 855 studies and BAX 855-naïve subjects.

Subjects are to receive either a fixed dose prophylaxis with BAX 855 consisting of 45 ± 5 IU/kg for subjects aged ≥ 12 years or 50 ± 10 IU/kg for subjects aged < 12 years (in all countries except the Russian Federation) twice weekly or, subjects can decide to receive a pharmacokinetic (PK)-tailored prophylactic BAX 855 dosing regimen based on the subject's individual PK to maintain FVIII trough levels of ≥ 3%. Other treatment regimens were allowed prior to protocol amendment four.

Subjects are to be treated on the specified prophylactic treatment regimen until they reach at least 100 exposure days (EDs) (as accumulated across all BAX 855 studies).

It is to be noted that the use of any FVIII concentrate other than BAX 855 during the course of the study following the first BAX 855 infusion is not permitted. The use of (commercial) ADVATE may be permitted for a short period of time for administrative reasons. It is also to be noted that ADVATE was allowed as rescue medication in

previous versions (prior to amenmdent four) of the protocol for this study under which a number of subjects have been enrolled.

2.1 Inclusion Criteria

Refer to Section 9.1 of the Clinical Study Protocol for information on inclusion criteria.

2.2 Exclusion Criteria

Refer to Section 9.2 of the Clinical Study Protocol for information on exclusion criteria.

2.3 Sample Size and Power Calculations

In total, approximately 250 subjects are to be enrolled in this study. The sample size is based on having 200 evaluable subjects with a minimum of 100 EDs to BAX 855 in accordance with the guidance EMA/CHMP/BPWP/144533/2009.

2.4 Randomization and Blinding

This is a non-randomized, open-label, active treatment clinical study.

2.5 Study Stopping Rules

Refer to Section 8.6 of the Clinical Study Protocol for information on study stopping rules.

2.6 Study Assessments

Refer to Section 20.3 of the Clinical Study Protocol for a schedule of study procedures and assessments.

2.7 Data Monitoring Committee

A Data Monitoring Committee (DMC) is not to be used for this study as the expected related AEs in this study are anticipated to be similar to that 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 and pediatric studies (Studies 261201 and 261202, respectively).

3. STUDY OUTCOME MEASURES

3.1.1 Primary Outcome Measures

3.1.1.1 Safety

1. Development of inhibitory antibodies to FVIII.

3.1.1.2 Efficacy

1. Spontaneous ABR.

3.1.2 Secondary Outcome Measures

3.1.2.1 Efficacy

1. Total ABR (spontaneous and traumatic bleeding episodes).

2. Overall hemostatic efficacy rating of BAX 855 for treatment of breakthrough bleeding episodes.

3. Number of BAX 855 infusions to treat bleeding episodes.

4. Time intervals between bleeding episodes.

5. Weight-adjusted consumption of BAX 855.

3.1.2.2 Safety

1. Occurrence of AEs and serious AEs (SAEs).

2. Changes in vital signs and clinical laboratory parameters (hematology, clinical chemistry, and lipids).

3. Immunogenicity

    a. Binding antibodies [immunoglobulin (Ig) G (IgG) and IgM] to FVIII, polyethylene glycol (PEG)-FVIII, and PEG.

    b. Anti-Chinese hamster ovary (CHO) antibodies.

3.1.2.3 Patient Reported Outcomes

Changes from baseline in parent study, if applicable, in the following:

1. Bleed and pain severity as measured using the haemophilia symptoms (Haemo-SYM) questionnaire.

2. Health related quality of life (HRQoL) as assessed using the short form-36 (SF-36)/Pediatrics Quality of Life (PedsQL) questionnaires.

3.1.3 Exploratory Outcomes Measure

1. Patient satisfaction with treatment is to be assessed using the Satisfaction Question Set.

2. Patient Activity Level.

3. Health resource use data (e.g., physician office visits, hospitalizations, days missed from work/school).

4. TGA parameters, FVIII trough levels and ABR.

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 to be 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 are to be performed on the SAS.

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

- *Study Infusion* eCRF panels.
- *Infusion for Determination of Incremental Recovery* eCRF panels.
- *Infusion for PK Assessment* eCRF panels.
- *Minor Surgery* eCRF panels.

4.3 Full Analysis Set (FAS)

The full analysis set (FAS) is to comprise of all subjects in the SAS.

4.4 Per Protocol Analysis Set (PPAS)

The per protocol (PPAS) analysis set is to comprise all subjects in the FAS who had no major deviations from the protocol affecting the study results. Protocol deviations are to be obtained from the Clinical Trial Management System (CTMS).

Prior to performing any analysis as set out in this SAP, a meeting is to be held discussing the impact of any major protocol deviation on the analysis. At this meeting, the decision is to be made on whether a subject is to be excluded from the PPAS analysis set or not. The meeting is to be attended by participants from at least Biostatistics and Medical.

Below is a list of possible major deviations that may influence the study results that will be discussed at the analysis set assignment meeting:

- Subject less than 75% exposed to BAX 855 as derived in Section 6.8: Measurements of Treatment Compliance.
- Subject less than 75% compliant to planned dosing regimen.
- More than 10% of treated bleeds have no efficacy rating.
- Use of expired IP.
- Subject did not reach 100 EDs across all BAX 855 studies.
- Use of any FVIII product other than ADVATE, as determined by the medical team.

It should be noted that the above will not necessarily lead to immediate exclusion from the PPAS, but will be discussed prior to locking the database. The database is not allowed to be locked until final approval on the PPAS has been obtained.

During the course of the study, data review meetings are to be held on a regular basis. During these meetings the quality of the data including any potential protocol deviations are to be identified. All protocol deviations identified at these meetings are to be included into the CTMS upon team agreement.

4.5 Pharmacokinetic Analysis Set (PKAS)

The PK analysis set (PKAS) is to comprise of all subjects in the SAS with at least one PK assessment performed in the current study.

5. STATISTICAL CONSIDERATIONS

5.1 Interim Analyses

A first interim safety review is to be performed for license submission to the European Medicines Agency (EMA).

If applicable, a second interim safety review may be performed once 200 subjects have accumulated at least 100 EDs to BAX 855.

5.2 Final Analysis

The final planned analysis identified in this SAP is to be performed by IQVIA Biostatistics following Baxalta's authorization of this SAP and Database Lock.

The final analysis is to 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.
- All reconciliation of vendor data with eCRF data completed successfully.
- Analysis sets authorized.

It is to be noted that all verbatim text from the eCRF to be presented in any outputs are to be presented "as is" with no "manual hard coding" corrections for such data.

5.3 Reference Start Date and Study Day

Reference start date is defined as the day of the subject's first BAX 855 infusion in the 261302 protocol (henceforth referred to as the current study) and is to be referred to as Day 1. Subjects that discontinue study participation prior to receiving any BAX 855 dose in the current study will not have a reference start date.

Study Day is to be calculated as described below from the reference start date (first BAX 855 infusion in the current study), and is to be used to show start and stop day of assessments and events.

- If the date of the event is on or after the reference date then:

$$Study\ Day = (Date\ of\ Event - Reference\ Date) + 1$$

- If the date of the event is prior to the reference date then:

$$Study\ Day = (Date\ of\ Event - Reference\ Date)$$

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

5.4 Handling of Missing, Unused, and Spurious Data

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

Exposure:

Should body weight (as obtained from the *Vital Signs* eCRF panels) be missing for a subject at the time of study infusion, the latest available body weight measurement at the time of the infusion is to be carried forward in order to compute body weight-adjusted BAX 855 consumption.

Adverse Events:

- Handling of unknown causality assessment:
  - If a subject experiences an AE with a missing causality assessment, the relationship of the AE is to be considered as "related".
- Handling of unknown severity grades:
  - If a subject experiences more than one AE categorized under the same preferred term, one of them is categorized as "severe" and one of them is categorized as "unknown", then the severity of the AE is to be counted as "severe".
  - If a subject experiences more than one AE categorized under the same preferred term, one of them is categorized as "mild" or "moderate" and one of them is categorized as "unknown", then the severity of the AE is to be counted as "unknown".

Laboratory Data:

Imputation of below limit of quantification (BLQ) and above limit of quantification (ALQ) results are described in the applicable analysis sections.

5.5 Definition of Baseline

Except for quality of life analyses, 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 and Study Day. If the date of the last non-missing assessment and the reference start date coincide, the assessment is to be considered baseline. Baseline for quality of life analyses is defined in Section 9: EVALUATION OF PATIENT REPORTED OUTCOMES.

For subjects transitioning to the Continuation study from another BAX 855 study where no result prior to first administration of BAX 855 in the current study is available, the last possible results from the study transitioned from will be used as baseline. The exception would be for height where the Screening result from the predecessor study will be used.

5.6 Definition of Visit Windows

All data is to be presented by nominal visit date as recorded on the eCRF. Visits are not to be reassigned from the recorded nominal visit to any other visit based on dates.

5.7 Changes from the Planned Statistical Analysis in Protocol

The following changes from the analyses planned in the Protocol have been made:

- The protocol mentions that no missing data is to be imputed. Imputations for certain missing data items have been allowed for though (refer to Section 5.4: Handling of Missing, Unused, and Spurious Data).
- The protocol mentions one generalized estimating equation (GEE) model to be fit for ABR. Due to the difference in treatment regimens between protocol amendments, this has been adjusted to model twice weekly fixed dose regimen and PK-tailored regimen separately from the every 5 and 7 day treatment regimens.

5.8 Statistical Tests

The default significance level is to be 5%; confidence intervals are to be 95% and all tests are to be two-sided, unless otherwise specified in the description of the particular analyses.

P-values obtained from statistical inference tests are to be presented using four decimal places. P-values smaller than 0.0001, are to be presented as “<0.0001” and p-values

larger than 0.9999, but les than 1, are to be presented as ">0.9999". A p-value of exactly 1 is to be presented as "1.0000".

Unless otherwise specified the default summary statistics for quantitative variables are to 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 is to be presented as "Not reported" where applicable. A "Not reported" category is only to be presented should there be unavailable results. No distinction based on the reason for unavailable results are to be made in 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, unless data warrants the use of more decimals):

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

For qualitative variables the number (n) and percentage (%) of subjects in each category are to be the default summary presentation. Unless otherwise specified, percentages are to be calculated relative to the total number of subjects in the relevant analysis set as described in the latest version of the Output Templates. In the event of unavailable assessments a "Not reported" category is to be presented. A "Not reported" category is only to be presented if applicable. The "Not reported" category is to 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 are to be made in any presentations.

All values are to be rounded using the SAS® function ROUND. All computed percentages are to be presented using one decimal place.

5.9 Common Calculations

For quantitative measurements, change from baseline is to be calculated as:

$$Change\ from\ Baseline\ at\ Visit\ X = Test\ Value\ at\ Visit\ X - Baseline\ Value$$

5.10 Multicenter Studies

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

Unless otherwise specified, all summaries are to be produced overall and is not to be summarized by center.

5.11 Examination of Subgroups

The following subgroups are to be used in analyses as indicated in the latest version of the Output Templates:

- Treatment regimen at any time in the study as obtained from the *Treatment Assignment* and *Change in Treatment Assignment* eCRF forms:
  - Fixed dose prophylactic treatment regimen.
  - PK-tailored prophylactic treatment regimen.
- Age groups [years] (per different regional standards), using age at informed consent as obtained from the *Demographics* eCRF form:
  - United States (US) age groups [years]:
    - Age < 2.
    - Age ≥ 2 to <12.
    - Age ≥ 12 to <17.
    - Age ≥ 17.
  - European (EU) age groups [years]:
    - Age < 6.
    - Age ≥ 6 to <12.
    - Age ≥ 12 to <18.
    - Age ≥ 18.
- Target joints at Screening as obtained from the *Hemophilia A History/Blood Group/Family History/Target Joint Identification* eCRF form:
  - Present.
  - Absent.

- Number of bleeds during the study as obtained from the *Bleeding Episodes* eCRF forms:
    - No bleeds during the study.
    - At least one bleed during the study.
- Treatment regimen prior to entering the Continuation study as obtained from the *Hemophilia A Treatment History* eCRF form:
    - Prophylactic regimen.
    - On-demand treatment.

5.12 Multiple Comparisons/Multiplicity

Not applicable.

6. STUDY SUBJECTS

6.1 Disposition of Subjects

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

Each subject is to participate in the study until a total of at least 100 EDs to BAX 855 have been achieved (accumulated across all BAX 855 studies in which each subject participated in).

Depending on the subject's BAX 855 exposure history and treatment regimen given, the planned duration of subject participation to reach the 100 EDs vary from approximately three to 12 months.

The following information is to be obtained from the eCRF:

- Informed consent (*Informed Consent* eCRF panels).
- Protocol version the subject enrolls onto the study (*Protocol Version* eCRF panels).
- Inclusion and exclusion criteria met and/or not met (*Inclusion/Exclusion Criteria* eCRF panels).
- Visit dates (*Date of Visit* eCRF panels).
- Other studies in the BAX 855 program the subject participated in (*Demographics* eCRF panels).
- Study completion (*Completion/Termination* eCRF panels):
- AE term and number (*Adverse Event* eCRF panels).
- Transfer to surgery study (if applicable; *Transfer to Surgery Study* eCRF panels).

- Return from surgery study (if applicable; *Return from Surgery Study* eCRF panels).
- Treatment regimen including date of treatment regimen start (*Treatment Regimen* and *Change in Treatment Regimen* eCRF panels).
- BAX 855 administration (*Study Infusions* eCRF panels).

The following derivations based on eCRF reported results are to be performed:

- A subject is considered to be enrolled if date of informed consent is present.
- A subject is to be assigned as dosed with a particular treatment regimen if the subject received any BAX 855 infusion when assigned to the particular regimen. Treatment regimen assignments are described in Section 5.11: Examination of Subgroups.
- A subject is considered to be completed if the reason for termination indicates the subject completed the study. Otherwise the subject is to be considered discontinued.

Planned presentation of tables on the disposition of subjects are to include a summary of disposition and analysis sets on the ENR set.

Planned presentation of listings on the disposition of subjects are to include information on previous BAX 855 studies participated in, disposition in current study, information on informed consent and eligibility, visit dates and analysis sets on the ENR set. Further listings are to include information on transfer and return from surgery study for subjects that did transfer to the surgery study.

6.2 Demographic and Baseline Characteristics

The following information is to be reported in the eCRF for demographic and baseline characteristics:

- Demographics (*Demographics* eCRF panels).
- Height and weight at Screening (*Vital Signs* eCRF panels).
- Information on hemophilia A history, blood group, family history and target joint identification at Screening (*Hemophilia A History/Blood Group/Family History/Target Joint Identification* eCRF panel).
- Estimated total number of documented previous FVIII EDs and average ABR based on previous three to six months (*Hemophilia A Treatment History* eCRF panel).

Should height not be recorded in the current study, height will be obtained from the Screening results of the predecessor study.

The following information is to be 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 hemophilia arthropathy.
- Categorization of gene mutation for use in summaries.

The following information is to be obtained from the central laboratory:

- Hepatitis C virus antibody and HIV results at Screening.

The following derivations based on eCRF reported results are to be performed:

- Race is to be presented as 'Multiple' in summaries if more than one race is selected on the eCRF.
- Body mass index (BMI) is to be derived as:

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

- The number of target joints at Screening are to be counted from the eCRF.
- The number of target joints at Screening are to be counted from the eCRF.
- Average ABR based on previous three to six months are to 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.
- The presence of hemophilia arthropathy is to be determined as present if any medical history is present that can be considered as hemophilia arthropathy, otherwise is to be determined as absent.

Planned presentations of tables on demographic and baseline characteristics are to include baseline demographics and disease characteristics for the SAS, FAS and PPAS.

Subgroup analyses on demographic and baseline characteristics are to be performed by age, presence or absence of target joints at screening, initial treatment regimen in this study, and treatment regimen prior to entering the Continuation study.

Planned presentation of listings on demographic and baseline characteristics are to include baseline demographics and hemophilia A history, blood group and target joint specification at Screening for the SAS.

6.3 Medical History

Information on medical history is to be obtained from the eCRF (*Medical History* eCRF panels).

Medical histories are to be listed and summarized for the SAS. Medical history summaries are to be presented by age category.

6.4 Hemophilia A Treatment History

Information on hemophilia A treatment history is to be obtained from the eCRF (*Hemophilia A Treatment History* eCRF panel).

Hemophilia A treatment history is to be listed for the SAS. No summaries are to be presented for hemophilia A treatment history.

6.5 Prior PEGylated Medication History

Information on prior PEGylated medication is to be obtained from the eCRF (*Prior Pegylated Medication History* eCRF panel).

PEGylated medications are to be coded using the World Health Organization – Drug Dictionary Extended Version (WHO-DDE) as documented in the Data Management documentation at the time of performing the analysis.

Prior PEGylated medications are to be listed for the SAS. No summaries are to be presented for prior PEGylated medications.

6.6 Prior and Concomitant Medications and Non-drug Therapies

Information on prior and concomitant medications and non-drug therapies is to be obtained from the eCRF (*Concomitant Medications/Non-drug Therapies* eCRF panels). Information on AEs and medical histories for which the medication or non-drug therapy has been given, is to be obtained from the eCRF (*Adverse Event* and *Medical History* eCRF panels).

Medications are to be coded using the WHO-DDE as documented in the Data Management documentation at the time of performing the analysis.

The following derivations based on eCRF reported results are to be performed:

- Assignment to Prior or Concomitant:
    - A medication or non-drug therapy is to be assigned as 'Prior' if the medication or non-drug therapy stopped prior to first BAX 855 administration in the current study.
    - A medication or non-drug therapy is to be assigned as 'Concomitant' if the medication or non-drug therapy:
        - Started after first BAX 855 administration in the current study; or
        - Started before the first BAX 855 administration in the current study and ended after first BAX 855 administration in the current study or is still ongoing.
    - A medication or non-drug therapy is to 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 is to be obtained linking the information from the particular eCRF panels.

Medications and non-drug therapies are to be listed for the SAS. No summaries are to be presented on medications or non-drug therapies.

6.7 Extent of Exposure

The following information is to be obtained from the eCRF:

- Information on study infusions (*Study Infusions* eCRF panels).
- Treatment regimen, including planned dose (*Treatment Assignment* and *Change of Treatment Assignment* eCRF panels).
- Body weight (*Vital Signs* eCRF panels).

The following derivations based on eCRF reported results are to be performed:

- Body weight-adjusted dose (IU/kg) is to be derived as the total units infused (IU) divided by the last available body weight (kg) prior to the infusion. Refer to Section 5.4: Handling of Missing, Unused, and Spurious Data for imputation schemes to be implemented.
- Total number of infusions in this study are determined as the count of the number of infusions, regardless of date and time, the subject had. Number of infusions are to be determined overall and by reason for infusion as well as by the treatment regimen assigned to at the time of receiving the treatment.
- The number of EDs are determined as the number of unique calendar days on which a subject received any or part of any infusion. Multiple infusions on the same day are still to be considered one ED. EDs are to be determined overall as well as for each reason an infusion is given. The number of EDs will be determined for this study and across all previous BAX 855 studies the subject participated in. EDs in this study will be derived as the number of infusions on unique calendar days in this study, while EDs from previous BAX 855 studies will be obtained as reported in the eCRF. The total EDs across all BAX 855 studies will be determined as the sum of EDs in current study and EDs in previous studies.
- The observation period for efficacy (OPE) in days in the study for subjects who never transferred to the surgery study is to be determined as:

$$OPE(Days) = (Stop\ Date - Start\ Date) + 1$$

  where "Start Date" refer to the first BAX 855 infusion in the current study and "Stop Date" to the last BAX 855 infusion in the current study. For subjects on the PK-guided regimen, first BAX 855 infusion will be the first prophylactic infusion.
- The OPE in days for subjects that did transfer to the surgery study is to be determined as:

$$\begin{aligned} OPE(Days) &= (Date\ of\ Transfer\ to\ Surgery\ Study - Start\ Date) \\ &+ (Stop\ Date - Return\ Date\ to\ Current\ Study) + 1 \end{aligned}$$

  where "Start Date" and "Stop Date" are defined as above.
- The OPE in weeks is to be determined from the OPE in days as:

$$OPE(Weeks) = \frac{OPE(Days)}{365.2425} \times 52$$

- The OPE in months is to be determined from the OPE in days as:

$$OPE(Months) = \frac{OPE(Days)}{365.2425} \times 12$$

- The OPE in years is to be determined from the OPE in days as:

$$OPE(Years) = \frac{OPE(Days)}{365.2425}$$

- All OPE calculations to be performed overall and per treatment regimen.
- The average number of infusions per time period (weeks, months, years) is to be determined as the total number of infusions during the observation period divided by the duration for the particular time period (weeks, months, years).
- Total dose (IU/kg or IU as applicable) is to 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) is to be determined as the total dose (IU/kg or IU as applicable) the subject received during the observation period in the current 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.

Extent of exposure is to be summarized using descriptive statistics for the SAS, and PPAS and listed for the SAS. Summaries are to be presented by age category and treatment regimen at time of dose.

6.8 Measurements of Treatment Compliance

Treatment compliance is to be derived using results and derivations obtained from study exposure as described in Section 6.7: Extent of Exposure.

Treatment compliance is to be based on the following:

- Adherence to the infusion schedule; and
- Adherence to recommended prophylactic dose.

An infusion is considered to be in adherence to the infusion schedule if:

- Time since last infusion on the “twice weekly regimen” do not exceed 5 days.
- Time since last infusion on the “every 5 day regimen” do not exceed 5 days.
- Time since last infusion on the “every 7 day regimen” do not exceed 7 days.
- Time since last infusions on the “other dosing regimen” do not exceed the days specified by the investigator.

Based on the treatment regimen, time that a subject was not exposed to BAX 855 is to be determined. Time a subject was not exposed to BAX 855 is to be derived as:

$$\begin{aligned} &Time\ not\ Exposed\ (Days) \\ &\quad = Days\ since\ last\ BAX\ 855\ infusion \\ &\quad - Treatment\ regimen\ allowed\ days \end{aligned}$$

Time not exposed (days) is to be set to 0 days if the above derivation results in number of days less than 0. The total time not exposed to BAX 855 for each subject will be determined as the sum of times not exposed for each individual infusion.

The percentage of time a subject was exposed to BAX 855 is to be derived as follows:

$$Time\ Exposed\ (\%) = \frac{OPE(Days) - Total\ Time\ not\ Exposed\ (Days)}{OPE(Days)} \times 100$$

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

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

Treatment compliance are to be summarized for the SAS and PPAS and listed for the SAS. Summaries are to be presented by age category and treatment regimen at time of dose on a subject level.

6.9 Protocol Deviations

Information on protocol deviations are to be obtained from the eCRF (*Protocol Deviations* eCRF panel).

Protocol deviations are to be summarized by classification (major or minor) presenting the number of deviations and the number of subjects having the particular deviation. Protocol deviations are to be summarized for the ENR by age group.

All protocol deviations are to be listed for the ENR.

7. EFFICACY EVALUATION

7.1 Bleeding Episodes

Results on spontaneous ABR are considered one of the co-primary objectives of this study. All other results related to bleeding episodes form part of the secondary objectives of this study.

The following information is to be obtained from the eCRF:

- Bleeding episodes (*Bleeding Episode* eCRF panels).
- Target joints (*Hemophilia A History/ Blood Group/ Family History/ 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 based on eCRF reported results are to be performed:

- 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.
    - Any free text identified anatomical bleeding site containing the word "Joint". Confirmation from medical is to be obtained on all free text identified joints prior to analysis.
- A joint is considered to be a target joint if:
    - The joint is identified as a target joint from either of the *Hemophilia A History/ Blood Group/ Family History/ Target Joint Identification* and *Development of new Target Joints* eCRF panels.

  - There was at least three spontaneous bleeds within six months in the particular joint.
  - A joint will cease to be considered as a target joint if identified in the eCRF with less than three spontaneous bleeds within a six month period.
- A bleeding site is considered to be a target joint if the specific joint is considered to be a target joint at the time of the bleed.
- A bleeding site is considered to be a non-target joint if the specific bleed is not considered to be a target joint at the time of the bleed. The bleeding site is still to be considered a joint.
- A bleed is considered to be an injury related bleed if the cause is indicated as "Injury"
- A bleed is considered to be a spontaneous bleed if the cause of bleed is identified as "Spontaneous" or "Unknown" in the eCRF.
- A bleed is considered to be a major bleed if the severity is indicated as "Severe" or "Major".
- A bleed is considered to be a moderate bleed if the severity is indicated as "Moderate".
- A bleed is considered to be a minor bleed if the severity is indicated as "Mild" or "Minor".
- A bleed is considered to be a weekday bleed if the bleed occurred on a Monday, Tuesday, Wednesday, Thursday or Friday.
- A bleed is considered to be a weekend bleed if the bleed occurred on a Saturday or Sunday.
- A bleed is considered to be a morning bleed if the bleed occurred between 04:00 and 11:59.
- A bleed is considered to be an afternoon bleed if the bleed occurred between 12:00 to 17:59.
- A bleed is considered to be 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 is to be derived as:

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

  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 bleed. Time since last prophylactic dose is to be categorized as:
  - <24 hours.

- 24 - <48 hours.
- 48 - <72 hours.
- 72 - <96 hours.
- ≥96 hours.

- Time since previous bleed are only to be determine if a subject had multiple bleeds and is to be derived as:

$$Time(months) = (Date/Time\ of\ Current\ Bleed - Date/Time\ of\ Previous\ Bleed)/365.2425 \times 12$$

- A bleed is considered to be 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" are not to 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), severity (mild, moderate and severe) and timing (weekends, weekdays, morning, evening and afternoon) are to be determined as the count of unique bleeds in each category a subject had during the observation period.
- Annualized bleeding rate (ABR) is to be derived for each treatment regimen the subject had during the study as:

$$ABR = \frac{Number\ of\ unique\ bleeds}{OPE\ (years)\ for\ treatment\ regimen}$$

The ABR is to be analyzed using a generalized linear model fitting a negative binomial distribution with logarithmic link function. Only subjects that have 100 or more EDs are to be included in the models, where total EDs are derived as in Section 6.7: Extent of Exposure.

The model is to be analyzed separately for each of the every 5 days and every 7 days treatment regimen. Baseline age and ABR as continuous covariate and the logarithm of the OPE in years, specific to each treatment regimen, as an offset, is to be included in the model. The following SAS® code is to be used to perform the analysis:

```
PROC GENMOD DATA = <ds>;
  MODEL <bleeds> = <baseline_age> <baseline_ABR> / DIST = NEGBIN
   OFFSET = <log_OPE> LINK = LOG;
  LSMEANS <regimen> / BYLEVEL OM CL;
  ODS OUTPUT LSMEANS = <outds>;
RUN;
QUIT;
```

where <ds> refers to the input dataset, <regimen> the particular treatment regimen time of bleed, <bleeds> the number of bleeds during the observation period, <baseline_age> the age at baseline, <baseline_ABR> the ABR at baseline and <log_OPE> the logarithm of the OPE in years, specific to the treatment regimen. Point estimates and confidence intervals obtained from the generalized linear model are to be anti-logged prior to presentation.

The twice weekly regimen and PK-tailored regimen will be analyzed together (not separately as per above model) using a generalized estimating equation (GEE) model using the following SAS® code:

```
PROC GENMOD DATA = <ds>;
  CLASS <subject> <regimen>;
  MODEL <bleeds> = <regimen> <baseline_age> / DIST = NEGBIN
   OFFSET = <log_OPE> LINK = LOG;
  REPEATED SUBJECT = <subject> / CORR = EXCH;
  LSMEANS <regimen> / BYLEVEL OM CL;
  ODS OUTPUT LSMEANS = <outds>;
RUN;
```

where <ds>, <regimen>, <bleeds>, <baseline_age> and <log_OPE> is define the same as before and <subject> is the subject number.

For both models above, should the model not converge a poisson model will be fitted instead. Should the non-convergence be due to all bleeds equal to zero, the estimate will be presented as zero with no confidence interval.

The model results are to be presented on the FAS and PPAS for:

- The total ABR.
- Annualized joint bleeding rate.
- Annualized non-joint bleeding rate.
- Annualized target joint bleeding rate.
- Annualized non-target joint bleeding rate.
- Annualized injury related bleeding rate.
- Annualized spontaneous/unknown bleeding rate.
- Annualized severe bleeding rate.
- Annualized moderate bleeding rate.
- Annualized minor bleeding rate.
- Annualized weekday bleeding rate.

- Annualized weekend bleeding rate.
- Annualized morning bleeding rate.
- Annualized afternoon bleeding rate.
- Annualized night bleeding rate.
- Annualized bleeding rate at unknown time.

A figure presenting results from the generalized linear model on the total ABR is to be presented for the FAS. Figures are also to be presented showing the number of bleeds within a specific time category since previous prophylactic infusion as well as bleeds overlaid with all treatments received during the study and binding antibodies on the FAS.

ABR for the above categories is to be presented descriptively for the FAS and PPAS. Descriptive statistics on the average duration between bleeding episodes for subjects with more than one bleeding episode and characteristics of bleeding episodes (including number of infusions to treat each bleed, total dose [IU] to treat each bleed, average dose per infusion to treat each bleed [IU/kg], efficacy rating, time since previous prophylactic dose [h] and severity of each bleed) are to be presented for the FAS and PPAS as well. Summaries for bleeding episodes are to be presented by age category, presence of target joints at screening and treatment regimen at time of bleed. Descriptive summaries on the number of infusions to treat a bleed are to include the 95% confidence interval on the median number of bleeds. The 95% confidence interval on the median will be determined using the distribution-free confidence interval for the 50th percentile from the SAS® UNIVARIATE procedure.

Information on bleeding episodes including the course of target joints and ultrasound information is to be listed for the SAS.

7.2 Weight-adjusted Consumption of BAX 855

Weight-adjusted consumption of BAX 855 is discussed in Section 6.7 Extent of Exposure.

8. SAFETY EVALUATION

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

8.1 Adverse Events

The following information is to be obtained from the eCRF:

- AEs (*Adverse Events* eCRF panels).

- Date and time of BAX 855 administration (*Study Infusions* eCRF panels).
- Reason for not completing the study (*Study Completion/Termination* eCRF panels).

Adverse events are to be 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 based on eCRF reported results are to be performed:

- 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.
  - The eCRF question "When did event occur in relation to treatment with BAX 855?" has a response of any of the following:
    - During treatment.
    - Within 24 hours after last treatment.
    - After more than 24 hours from last treatment.
- Time since last BAX 855 infusion is to be determined as:

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

  where the date/time of last BAX 855 exposure are the last possible BAX 855 administration, regardless of reason, prior to the start of the AE. Time since last BAX 855 infusion is only to 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 is to 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 is to be determined as:

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

  The duration of an AE is to 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 any analyses described in this SAP, a list of all AEs in the database is to 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 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 question "Did the serious event result in death" is indicated as "Yes" or if the outcome in the eCRF is indicated as "Fatal".
- An AE is considered to be an allergic reaction if the question "Was this event considered to be an allergic reaction" is indicated as "Yes".
- An AE is considered to be a thrombotic event if the question "Is this a thrombotic event" is indicated as "Yes" in the eCRF.

AEs that occurred during or after BAX 855 are to be presented for the SAS. Summary tables are to indicate the number of subjects who experienced AEs as well as the number of AEs. Summaries for BAX 855 as indicated in the latest version of the Output Templates are also to include the rate of AEs per 100 infusions and rate of AEs per year. In addition, tables are to be prepared to summarize each AE by system organ class and preferred term, the number of subjects who experienced an AE at least once, the rate of subjects with AE(s), AEs per 100 infusions and AE rate per year. AE summaries by seriousness, severity and relationship are to be presented as well.

AE rate per 100 infusions is to be determined as the number of AEs divided by the total number of infusions (regardless of the reason the infusion was administered) in the study multiplied by 100.

AE rate per year is to be determined as the number of AEs divided by the OPE in years in the current study across all subjects.

All AEs for each subject, are to be listed for the SAS.

8.2 Clinical Laboratory Evaluations

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

Information from the Investigator on abnormal results is to be obtained from the eCRF (*Central Laboratory* eCRF panels).

The following derivations are to be performed based on results obtained from the central laboratory and eCRF:

- A result is considered to be 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 to be provided by the central laboratory.
- A result is to be considered clinically significant if indicated as such by the Investigator on the eCRF.
- Quantitative laboratory measurements reported as "<X", i.e., BLQ, or ">X", i.e., ALQ are to be presented in listings as "<X" or ">X" and summarized in summaries as "0" for "<X" and "X" for ">X".

The following laboratory parameters are to be included in all summaries:

- Hematology:
    - Hemoglobin, hematocrit, red blood cell count including differentials (i.e., basophils, eosinophils, lymphocytes, monocytes and neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) and platelet count.
- Clinical chemistry:
    - Sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine and glucose.
- Lipid panel:

  - Cholesterol, very low density lipoprotein (VLDL), low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides.
- Viral serology:
  - HIV-1Ab, HIV-2Ab, HBcAb, HBsAb, HBsAg and HCVab.

For hematology, clinical chemistry and lipid parameters, summary statistics on observed and change from baseline result and shift tables are to be presented for the SAS. Descriptive statistics on viral serology are to be presented for the SAS.

Descriptive statistics for laboratory results by visit are to be presented in a box-plot for the SAS.

Laboratory results for all parameters (planned or unplanned) are to be listed for the SAS, including separate listings for abnormal and clinically significant results.

8.3 Inhibitor/Antibody Development

FVIII inhibitory antibody development is considered one of the co-primary objectives of this study. Other antibody results are considered part of the secondary objectives of this study.

Results on inhibitory antibodies to FVIII and binding antibodies to FVIII, PEG-FVIII and PEG (both IgG and IgM) and anti-CHO antibodies are to be obtained from the central laboratory.

A subject is to be considered to have developed inhibitory antibodies to FVIII if the result obtained from the central laboratory are $\geq$ 0.6 BU.

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

Descriptive statistics and listings on inhibitory antibodies to FVIII and binding antibodies to FVIII, PEG-FVIII and PEG and anti-CHO antibodies are to be presented for the SAS. Summaries are to be presented by age categories.

The proportion of subjects which developed inhibitory antibodies to FVIII at any time during the study is to be reported, together with exact Clopper-Pearson 95% confidence intervals for the proportion. The subset of subjects included in this analysis are:

- Subjects that developed inhibitory antibodies to FVIII at any time during the study; and
- Subjects that did not develop any inhibitory antibodies to FVIII but had 100 or more EDs to BAX 855 across all BAX 855 studies AND had a FVIII inhibitory antibody test result from the central laboratory after the 100th ED.

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

```
PROC FREQ DATA = <ds>;
  WEIGHT <count>;
  TABLES <result> / BINOMIAL (EXACT CP) ALPHA = 0.05 CL;
RUN;
QUIT;
```

where <ds> refers to the input dataset, <count> the number of subjects with particular result and <result> to the actual result, i.e., "Yes" or "No".

8.4 Vital Signs

Information for Vital Signs is to be obtained from the eCRF (*Vital Signs* eCRF panels).

The following derivations based on eCRF reported results are to be performed:

- A result is considered to be 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:

Parameter	Age Range (Years)			
	≥13	≥6 - <13	≥3 - <6	<3
Respiratory rate (breaths/minute)	12-20	14-22	20-25	20-30
Pulse rate (beats/minute)	60-90	60-95	65-110	70-110
Systolic blood pressure (mmHg)	90-120	100-120	95-110	90-105
Diastolic blood pressure (mmHg)	60-80	60-75	60-75	55-70
Body temperature	35-37.9	35-37.9	35-37.9	35-37.9

Parameter	Age Range (Years)			
	≥13	≥6 - <13	≥3 - <6	<3
(°C)				

Summary statistics on observed and change from baseline results are to be presented for vital signs on the SAS by age groups. All vital signs results are to be listed for the SAS.

8.5 Physical Examination

Information for physical examination is to be obtained from the eCRF (*Physical Examination* eCRF panels).

Physical examination results are to be listed for the SAS. No summaries on physical examination are to be presented.

8.6 Comments

Information for comments is to be obtained from the eCRF (*General Comments* eCRF panel).

Comments are to be listed for the ENR. No summaries on comments are to be presented.

9. EVALUATION OF PATIENT REPORTED OUTCOMES

For all patient reported outcomes baseline are to be defined as:

- The baseline measurement for the particular questionnaire in the parent study (i.e., the first study participated in the BAX 855 program of studies); OR
- For BAX 855 naïve subjects or subjects with no baseline results available in the parent study, the first questionnaire results prior to first dose in the current study are to be defined as baseline.

9.1 Haemophilia Symptom Questionnaire (Haemo-Sym)

The hemophilia symptom questionnaire (Haemo-Sym) is a self reported instrument of measuring symptom severity in patients with hemophilia and has two subscales: pain and bleeds.

Information on the Haemo-Sym is to be obtained from electronic patient diaries.

The questions in the Haemo-Sym questionnaire are to be assigned to the subscales of pain and bleeds as set out in Table 1:

Table 1 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
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 to be assigned scores as follows:

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

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

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

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 is to be calculated for that subscale.

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

The Haemo-Sym scores and changes from baseline are to be summarized for the FAS by treatment regimen and age category. The number and proportions of subjects with an improvement (defined as a decrease in Haemo-Sym score of greater than 1) is to be presented for the FAS. A Wilcoxon Signed-Rank test for paired samples is to be presented on the FAS comparing the baseline and study completion scores for any statistical significant differences. The following SAS® code is to be used to perform the Wilcoxon Signed-Rank test for paired samples:

```
PROC UNIVARIATE DATA = <ds>;
  VAR <Change>;
  ODS OUTPUT TestsForLocation=<outds> (WHERE = (test = 'Signed
Rank'));
RUN;
QUIT;
```

where <ds> refers to the input dataset, <Change> the change from baseline at the completion visit and <outds> the resulting dataset from the procedure.

Statistical significant differences are present between baseline and completion results if a p-value of <0.05 is obtained.

Haemo-Sym individual results and calculated scores are to be listed for the FAS.

9.2 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 to be obtained from electronic patient diaries.

The questions in the SF-36 are assigned to domains and scored as set out in Table 2.

Table 2 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?		
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

Question	Domain	Score
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)?		
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)	<u>If Question 7 Answered:</u> 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 <u>If Question 7 Not Answered:</u> 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
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 2, raw scores for each domain are to be calculated as set out in Table 3.

Table 3 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 score for each domain is then to 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 is to 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 are to be used to determine norm-based scores that are to be presented in listings and summaries. The norm based scores are to be determined as:

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

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

The raw aggregate summary scores for the physical and mental components are to be determined as follows:

- $AGG_{Phys} = (PF_z \times 0.42402) + (RP_z \times 0.35119) + (BP_z \times 0.31754) + (GH_z \times 0.24954) + (VT_z \times 0.02877) + \left(SF_z \times (-0.00753)\right) + \left(RE_z \times (-0.19206)\right) + \left(MH_z \times (-0.22069)\right)$
- $AGG_{Ment} = \left(PF_z \times (-0.22999)\right) + \left(RP_z \times (-0.12329)\right) + \left(BP_z \times (-0.09731)\right) + \left(GH_z \times (-0.01571)\right) + (VT_z \times 0.23534) + (SF_z \times 0.26876) + (RE_z \times 0.43407) + (MH_z \times 0.48581)$

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

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

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 is to be adjusted in terms of the lowest and highest possible score, including the possible raw range. All other scores are to be affected by this change in transformed score. As an example, say 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 are to be used in determining the transformed score for physical functioning.

The SF-36 scores and changes from baseline are to be summarized for the FAS by treatment regimen and age category. The number of subjects with an improvement (defined as an increase in SF-36 score greater than 1) are to be presented for the FAS. A Wilcoxon Signed-Rank test for paired samples is to be presented on the FAS comparing the baseline and study completion scores for any statistical significant differences using the SAS code provided in Section 9.1: Haemophilia Symptom Questionnaire (Haemo-Sym).

SF-36 individual results and calculated scores are to be listed for the FAS.

9.3 Pediatrics Quality of Life Questionnaire (PedsQL)

The pediatrics quality of life questionnaire (PedsQL) is a generic HRQoL instrument designed specifically for a pediatric population. The questionnaire consists of different questions based on the age of the subjects for ages 2-4, 5-7 and 8-12. The PedsQL capture data for the following domains: physical functioning, emotional functioning, social functioning, school functioning, psychosocial functioning, physical health and a total score.

Information on the PedsQL is to be obtained from electronic patient diaries.

The questions in the PedsQL are categorized as set out in Table 4.

Table 4 Categorizing Pediatric Quality of Life Questions

Category (Problems with…)	Toddler (Ages 2 -4)	Young Children (Ages 5-7)	Child Report (Ages 8-12)
Physical Functioning	Walking	Walking 100 meters	It is hard for me to walk more than a couple of streets (100 meters)
	Running	Running	It is hard for me to run
	Participating in active play and exercise	Participating in sports activities or exercise	It is hard for me to do sports activities or exercise
	Lifting heavy things	Lifting something heavy	It is hard for me to lift heavy things
	Bathing	Taking a bath or shower by him or herself	It is hard for me to have a bath or shower by myself
	Helping to pick up his or her toys	Doing chores, like picking up his or her toys	It is hard for me to do chores around the house
	Having aches or pains	Having aches or pains	I have aches and pains
	Feeling tired	Feeling tired	I feel tired.
Emotional Functioning	Feeling afraid or scared	Feeling afraid or scared	I feel afraid or scared

Category (Problems with…)	Toddler (Ages 2 -4)	Young Children (Ages 5-7)	Child Report (Ages 8-12)
	Feeling sad	Feeling sad	I feel sad
	Feeling angry	Feeling angry	I feel angry
	Having trouble sleeping	Trouble sleeping	I have trouble sleeping
	Worrying	Worrying about what will happen to him or her	I worry about what will happen to me
Social Functioning	Playing with other children	Getting on with other children	I have trouble getting on with other children
	Other children not wanting to play with him or her	Other children not wanting to be his or her friend	Other children do not want to be my friend
	Getting teased by other children	Getting teased by other children	Other children tease me
	Not able to do things that other children his or her age can do	Not being able to do things that other children his or her age can do	I cannot do things that other children my age can do
	Keeping up when playing with other children	Keeping up when playing with other children	It is hard to keep up when I play with other children
Nursery/Day Care Functioning	Doing the same nursery/day care activities as my peers		
	Missing nursery day/care because of not feeling well		
	Missing nursery/day care to go to the doctor or hospital		
School Functioning		Paying attention in class	It is hard to pay attention in class

Category (Problems with…)	Toddler (Ages 2 -4)	Young Children (Ages 5-7)	Child Report (Ages 8-12)
		Forgetting things	I forget things
		Keeping up with school activities	I have trouble keeping up with my school work
		Missing school because of not feeling well	I miss school because of not feeling well
		Missing school to go to the doctor or hospital	I miss school to go to the doctor or hospital

Each question of the PedsQL is to be scored as follows:

- Never: 100
- Almost never: 75
- Sometimes: 50
- Often: 25
- Almost always: 0

Scores for the categories of physical functioning, emotional functioning, social functioning and school functioning are to be derived as the mean of the individual question scores of available data. Missing data are not to be imputed. At least half of the questions in a particular score category needs to be answered for a score to be presented.

The psychosocial health summary score is to be derived as the mean of the individual questions for the emotional functioning, social functioning and school functioning categories. The physical health summary score is to be set equal to the physical functioning category score.

The PedsQL scores and changes from baseline are to be summarized for the FAS by treatment regimen and age category. The number of subjects with an improvement (defined as an increase in PedsQL score greater than 1) are to be presented for the FAS. A Wilcoxon test for paired samples is to be presented on the FAS comparing the baseline and study completion scores for any statistical significant differences using the SAS code provided in Section 9.1: Haemophilia Symptom Questionnaire (Haemo-Sym).

PedsQL individual results and calculated scores are to be listed for the FAS.

10. EVALUATION OF EXPLORATORY OUTCOME MEASURES

10.1 Patient Satisfaction Questionnaire

The patient satisfaction questionnaire is a non-validated measure that assesses the subject's level of satisfaction with their treatment. For BAX 855 naïve subjects and BAX 855 naïve surgery subjects, at the end of study visit, the questionnaire also assesses the subject's preference between his previous treatment prior to study and BAX 855.

Frequency statistics and listings on patient satisfaction questionnaire results are to be presented for the FAS.

10.2 Patient Activity Level

Patient activity levels are to be summarized and listed for the FAS.

10.3 Hospitalizations Due to Hemophilia A

Information on hospitalizations is to be obtained from the eCRF (*Other Hospitalizations* eCRF panel).

The following derivations based on eCRF reported results are to be performed:

- Duration of hospitalization in days:
  $Duration(Days) = (End\ Date\ of\ Hospitalization - Start\ Date\ of\ Hospitalization) + 1$

Annualized number of hospitalizations and annualized duration of hospitalizations in days are to be summarized by treatment group and age group for the SAS. All hospitalizations are to be listed for the SAS.

Results are to be annualized by dividing the OPE in years of each subject with results obtained during the course of the study.

10.4 Health Resource Use Other Than Hospitalizations

Information on health resource use including days unable to go to school/work, days unable to carry out usual activities, number of physician visits, number of clinical visits and number of emergency room visits are to be reported in electronic subject diaries.

Results are to be annualized by dividing the OPE in years of each subject with results obtained during the course of the study.

Information on other health resource usage is to be summarized for the FAS and listed for the SAS.

10.5 TGA Parameters, FVIII Trough Levels, Incremental Recovery and Comparisons against ABR

PK concentrations are to be obtained from the central laboratory and PK parameters based on the PK concentrations are to be derived by Baxalta. Further details on the calculation of PK parameters are to be documented separately.

PK concentrations and PK parameters for all analytes are to be summarized and listed for the PKAS.

Incremental recovery (IR) as derived below will be summarized for the SAF by visit including changes from baseline. IR will also be displayed graphically over time for each subject. All IR results will be reviewed by the medical team for plausibility. All IR results found not plausible by the medical team will be excluded from the analysis.

The following formula will be used to determine IR:

$$IR[(IU/dL)/(IU/kg)] = \frac{PostFVIII\ [IU/dL] - PreFVIII\ [IU/dL]}{Weight\ Adjusted\ Dose\ [IU/kg]}$$

where $PreFVIII$ is the last available FVIII measurement prior to dose and $PostFVIII$ the first FVIII measurement after dose.

FVIII trough levels and TGA results per subject are to be plotted in a scatter plot against the ABR of the three months after FVIII trough level and TGA measurement with a regression line overlaid on the individual points. The ABR of the three months after FVIII trough level and TGA measurement will be determined as described in Section 7.1: Bleeding Episodes and by counting the bleeds to the next scheduled visit (which is scheduled every three months).

11. ANALYSIS SOFTWARE

All data processing, summarization, and analyses are to utilize SAS® software package, Version 9.4. If the use of other software is warranted the final clinical study report (CSR) is to detail what software was used.

12. REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	2017 APR 06	New Document
2.0	2017 DEC 08	Added more details to the per protocol analysis set. Removed imputations for exposure data with missing information.
3.0	2018 APR 18	Removed the requirement that bleeds need to be 72 hours apart to be considered a unique bleed. Added provision for fitting poisson models when negative binomial models for ABR do not converge. Added additional details on the presentation of IR, including the derivation of IR. Updated the US specific age categories to be in line with US requirements. Removed ADVATE analysis set and all analyses related to this analysis set.