Statistical Analysis Plan

NCT Number: NCT02615691

Title: Phase 3, prospective, multi-center, open label study to investigate safety, immunogenicity, and hemostatic efficacy of PEGylated Factor VIII (BAX 855) in previously untreated patients (PUPs) < 6 years with severe hemophilia A (FVIII < 1%)

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STATISTICAL ANALYSIS PLAN

BAX 855 – PEGylated full-length recombinant factor VIII

Phase 3, prospective, multi-center, open label study to investigate safety, immunogenicity, and hemostatic efficacy of PEGylated Factor VIII (BAX 855) in previously untreated patients (PUPs) < 6 years with severe hemophilia A (FVIII < 1%)

PROTOCOL IDENTIFIER: 261203

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ABBREVIATIONS

ABR	annualized bleeding rate
AE	adverse event
ALQ	above the upper limit of quantitation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BAX 855	PEGylated recombinant FVIII
BLQ	below the limit of quantitation
BU	Bethesda unit
BUN	blood urea nitrogen
CTMS	Clinical Trial Management System
DMC	data monitoring committee
ED	exposure day
eCRF	electronic case report form
ENR	all subjects enrolled set
FVIII	Factor VIII
HEAS	hemostatic efficacy analysis set
IAS	FVIII inhibitor treatment analysis set
IDAS	FVIII inhibitor detection analysis set
IEAS	FVIII inhibitor enrolled analysis set
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
INR	international normalized ratio
IP	investigational product
IPRAS	invasive procedure analysis set
ITI	immune tolerance induction
IQR	interquartile range
IR	incremental recovery
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NK	natural killer
PA4	Clinical Study Protocol Amendment 4
PA5	Clinical Study Protocol Amendment 5
PAS	prophylaxis analysis set
PEG	polyethylene glycol
PI	principal investigator
PK	pharmacokinetics

PKAS	pharmacokinetics analysis set
PUP	previously untreated patient
Q1	first quartile
Q3	third quartile
OPE	observation period for efficacy
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SI	standard international
Tfh	T follicular helper
Th	T helper
ULN	upper limit of normal
WHO-DD	World Health Organization – Drug Dictionary

1. INTRODUCTION AND OBJECTIVES

This document describes the rules and conventions to be used in the planned presentation and analysis of safety, immunogenicity and hemostatic efficacy data for Protocol 261203 as set out in the latest version of the Output Templates document. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This document, together with the Output Templates document, is to be used for both the interim and final analysis.

A separate data monitoring committee (DMC) statistical analysis plan (SAP) has been set up for DMC specific analyses.

The purpose of this study is to investigate safety, immunogenicity and hemostatic efficacy of PEGylated recombinant FVIII (BAX 855) in previously untreated patients (PUPs) < 6 years of age with severe hemophilia A (baseline FVIII level < 1%) and < 3 exposure days (EDs) to ADVATE, BAX 855 or plasma transfusion.

Subjects are being enrolled in different Clinical Study Protocol Amendments up to Protocol Amendment 8 (Global and EEA/UK versions). In PA5 the surgery and immune tolerance induction (ITI) sub-arms were removed to comply with regulatory requirements. It was still possible for subjects to develop inhibitors to Factor VIII (FVIII) in the EEA-specific PA5 and receive inhibitor treatment, but the terms “main study” and “ITI”, that were used in PA4, were removed for regulatory purposes. A subject in PA5 could still have surgery, but this is being referred to as invasive procedures and is not considered a sub-arm of the study.

1.1 Study Objectives

1.1.1 Primary Objective

The primary objective of this study is to determine the safety including immunogenicity of BAX 855 based on the incidence of inhibitor development to FVIII (≥ 0.6 Bethesda unit [BU]/mL using the Nijmegen modification of the Bethesda assay).

1.1.2 Secondary Objective(s)

1.1.2.1 Safety

- To determine the immunogenicity of BAX 855 in terms of binding immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies to FVIII, polyethylene glycol (PEG)-FVIII and PEG.
- To determine the safety of BAX 855 based on adverse events (AEs) and serious AEs (SAEs).

1.1.2.2 Hemostatic Efficacy

- To assess the efficacy of prophylactic treatment with BAX 855.
- To characterize the efficacy of BAX 855 in the control of bleeding episodes.
- To evaluate the efficacy of BAX 855 for perioperative management, if surgery is required (not applicable for PA8 EEA/UK v1).

1.1.2.3 Pharmacokinetics (PK)

- To determine incremental recovery (IR) of BAX 855 at baseline and over time.
- To determine half-life at baseline (optional).

1.1.2.4 Immune Tolerance Induction (ITI) Objectives (PA8 EEA/UK v1)

- To evaluate efficacy and safety of ITI with BAX 855.
- To determine the rate of success, partial success and failure of ITI with BAX 855.

1.1.3 Exploratory Objectives

- [redacted]
- [redacted].

[redacted]

2. STUDY DESIGN

This is a phase 3, prospective, open-label, multicenter study to assess the safety, immunogenicity and hemostatic efficacy of BAX 855 in PUPs < 6 years of age with severe hemophilia A (baseline FVIII level < 1%) and < 3 EDs to ADVATE, BAX 855 or plasma transfusion in at least 100 evaluable subjects. An evaluable subject is defined as a subject who has not developed inhibitors to FVIII and has 100 or more EDs to BAX 855 or who has developed inhibitors to FVIII confirmed by a second blood sample from central laboratory.

For Clinical Study Protocol Amendment 8 (PA8)
Subjects are to receive prophylactic and/or on demand therapy with BAX 855 for at least 100 EDs or until they have developed a confirmed FVIII inhibitor (Part A). During Part A, subjects can undergo surgical or invasive procedures under a protocol-defined regimen for BAX 855. Subjects who develop a high titer FVIII inhibitor (> 5.00 BU) or subjects with low titer FVIII inhibitors ((≥0.6 BU/mL but ≤5 BU/mL) where ITI therapy is necessary because of poorly controlled bleeding despite increased BAX 855 doses or bypassing agents are required to treat bleeding may enter Part B (ITI portion) of the study to undergo ITI therapy with BAX 855. Refer to Figure 1 for flow diagram of study design for PA8 (Global).

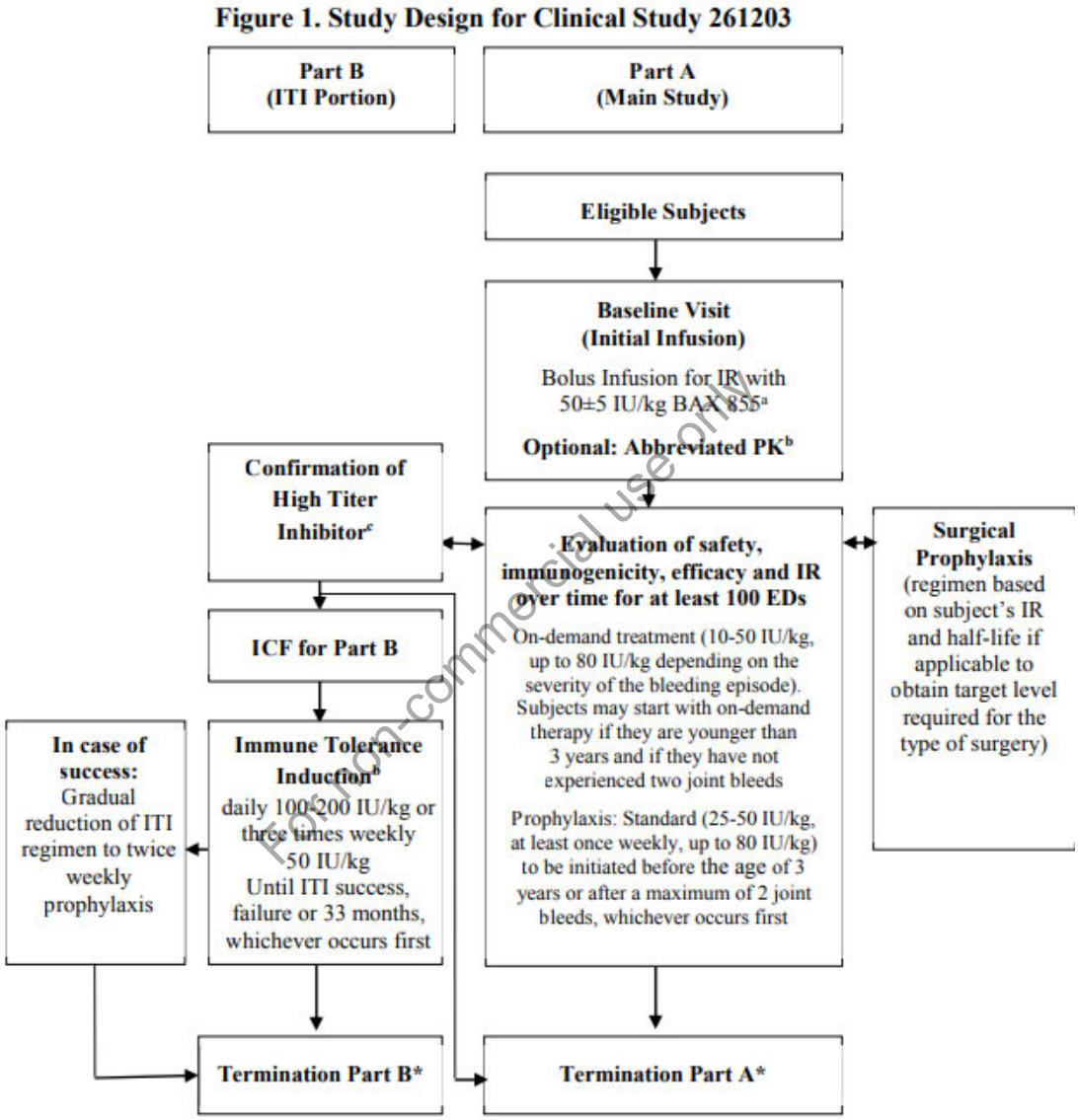
For Clinical Study Protocol Amendment 8 EEA/UK v1 (PA8 EEA/UK v1)
Subjects are to receive prophylactic and/or on demand therapy with BAX 855 for at least 100 EDs or until they have developed a confirmed FVIII inhibitor. In case of FVIII inhibitors, bypassing agents may be administered in addition to BAX 855. Refer to Figure 2 for flow diagram of study design for PA8 EEA/UK.

BAX 855 (commercial Adynovate/Adynovi) received before the study is not to be counted towards the 100 EDs.

The term “Main Study” is to indicate PA8 EEA/UK subjects in Part A and non-FVIII inhibitor PA8 (Global) subjects. The term “FVIII Inhibitor Treatment” is to indicate PA8

EEA/UK subjects in Part B and PA8 (Global) subjects that developed FVIII inhibitors and continue treatment with BAX 855.

Figure 1 Study Design for PA8 EEA/UK v1



[a] In case of on-demand or low-dose prophylaxis, a dose as low as 25 IU/kg may be administered for FVIII IR.
[b] Abbreviated PK for BAX 855 using 2 post-infusion timepoints: 15-30 minutes and 24-48 hours; may be performed at Baseline, Visit 1 or Visit 2
[c] Or low titer inhibitor with poorly controlled bleeding despite increased BAX 855 doses or requires bypassing agents to treat bleeding
* For optional extended access to BAX 855, refer to Section 8.3.

2.1 Study Population

PUPs < 6 years of age with severe hemophilia A (FVIII < 1%) and < 3 EDs to ADVATE, BAX 855 or plasma transfusion are to be studied.

2.2 Inclusion Criteria

Subjects who meet all of the following criteria are eligible for this study:

- Subject is < 6 years old at the time of screening.
- Subject is previously untreated with < 3 EDs to ADVATE, BAX 855 or plasma transfusion at any time prior to screening.
- Subject has severe hemophilia A (FVIII < 1%) as determined by the central laboratory, or a historical FVIII level < 1% as determined at any local laboratory, optionally supported by an additional FVIII gene mutation consistent with severe hemophilia A.
- Subject is immune competent with a CD4+ count > 200 cells/mm^3, as confirmed by the central laboratory at screening.
- Parent or legally authorized representative is willing and able to comply with the requirements of the protocol.

Additional inclusion criteria for immune tolerance induction (not applicable for PA8 EEA/UK v1):

- Parent or legal representative has/have voluntarily provided signed informed consent for ITI portion.
- Subject has a confirmed positive high titer inhibitor (> 5.00 BU) or has a positive confirmed low titer inhibitor (≥ 0.6 BU) as determined by the central laboratory based on a second repeat blood sample with,
    - poorly controlled bleeding despite increased BAX 855 doses, or
    - requires bypassing agents to treat bleeding episodes.

2.3 Exclusion Criteria

Subjects who meet any of the following criteria are not eligible for this study:

- Subject has detectable FVIII inhibitory antibodies (≥ 0.6 BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening.

- Subject has a history of FVIII inhibitory antibodies (≥ 0.6 BU using the Nijmegen modification of the Bethesda assay or the Bethesda assay) at any time prior to screening.
- Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (e.g., qualitative platelet defect or von Willebrand's disease).
- Subject has been previously treated with any type of FVIII concentrate other than ADVATE or BAX 855, or was administered ADVATE, BAX 855 or plasma transfusion for ≥ 3 EDs at any time prior to screening.
- Subject receives >2 EDs of ADVATE in total during the periods prior to enrollment and during the screening period, up until the baseline infusion.
- The subject's weight is anticipated to be < 5 kg at the baseline visit.
- Subject's platelet count is < 100,000/mL.
- Subject has known hypersensitivity towards mouse or hamster proteins, PEG or Tween 80.
- Subject has severe chronic hepatic dysfunction (e.g., > 5 times the upper limit of normal [ULN] alanine aminotransferase [ALT], aspartate aminotransferase [AST], or a documented international normalized ratio [INR] > 1.5) in his medical history or at the time of screening.
- Subject has severe renal impairment (serum creatinine > 1.5 times the upper limit of normal).
- Subject has current or recent (< 30 days) use of other PEGylated drugs prior to study participation or is scheduled to use such drugs during study participation.
- Subject is scheduled to receive during the course of the study a systemic immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day, or α-interferon) other than anti-retroviral chemotherapy.
- Subject has participated in another clinical study involving an investigational product (IP) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
- Parent or legally authorized representative has a medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance.
- Parent, legally authorized representative or subject are a member of the team conducting this study or is in a dependent relationship with one of the study team

members. Dependent relationships include close relatives (i.e., children, partner/spouse, siblings, parents) as well as employees of the investigator or site personnel conducting the study.

Additional exclusion criteria for immune tolerance induction (not applicable for PA8 EEA/UK v1):

- Spontaneous disappearance of the inhibitor prior to ITI.
- FVIII inhibitor titer ≥ 0.6 BU is not confirmed by a second new blood sample drawn within 2 weeks of study site notification of inhibitor and determined at the central. laboratory.
- Inability or unwillingness to comply with the protocol.

2.4 Sample Size and Power Calculations

The sample size of 100 subjects followed for 100 EDs originates from EMA/CHMP/BPWP/144533/2009; it is not based on statistical considerations. Since the targeted accrual is at least 100 subjects, approximately 120 subjects are to be dosed to allow for dropouts.

2.5 Randomization and Blinding

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

2.6 Study Stopping Rules

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

- If two or more subjects develop anaphylaxis following exposure to BAX 855.

The study may be terminated, or a study arm discontinued, 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.

2.7 Study Assessments

Refer to Table 6 – Table 11 in PA8 (Global) and Table 3 – Table 6 in PA8 EEA/UK v1 of the Clinical Study Protocols for the schedule of study procedures and assessments.

2.8 Data Monitoring Committee (DMC)

This study is to be monitored by a DMC. The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. For this study, the DMC is to be composed of recognized experts in the field of hemophilia clinical care and research who are not actively recruiting subjects. The DMC can stop a trial if it finds toxicities or if treatment is proven to be not beneficial.

The sponsor is to formally convene this panel for review of the study data at least once per year until completion of the study. (After the first DMC meeting, the frequency for DMC meetings was changed from once a year to twice a year.) Ad hoc convocations of the DMC are to occur on an as-needed basis. If the inhibitor incidence is above 41% of the total study cohort (the 95% confidence interval upper limit of that observed in the ADVATE PUP study) after at least the first 10 subjects are enrolled, then the data are to be presented to the DMC for review. Data from the laboratory are to be sent to IQVIA Biostatistics monthly to determine if the inhibitor incidence is above 41% of the total study cohort. This is done by comparing the number of subjects with two consecutive FVIII results from laboratory within 2 weeks after the first positive results ≥ 0.6 BU to the total number of subjects enrolled.

3. STUDY OUTCOME MEASURES

3.1 Primary Outcome Measure

The primary outcome measure is the incidence of FVIII inhibitor development.

3.2 Secondary Outcome Measures

3.2.1 Safety

- Binding IgG and IgM antibodies to FVIII, PEG-FVIII and PEG.
- AEs and SAEs.
- Clinically significant changes in vital signs and clinical laboratory parameters (hematology and clinical chemistry).

3.2.2 Efficacy

- Annualized bleeding rate (ABR) for prophylactic and on-demand treatment.
- Number of BAX 855 infusions per bleeding episode.
- Overall hemostatic efficacy rating at 24 h after initiation of treatment and at resolution of bleed.
- Weight-adjusted consumption of BAX 855 per month, per year and per event (prophylaxis, treatment of bleeding episode and surgery [not applicable for PA8 EEA/UK v1]) and the number of infusions per month and per year.
- Assessment of intra-, post- and perioperative hemostatic efficacy in case of surgery (not applicable for PA8 EEA/UK v1).
- Intra- and postoperative blood loss in case of surgery (not applicable for PA8 EEA/UK v1).

3.2.3 Pharmacokinetics

- IR at baseline and over time.
- Half-life at baseline (optional). This is to be based on an abbreviated PK using two post-infusion timepoints: 15 – 30 minutes and 24 – 48 hours.

3.2.4 Additional Outcome Measures for Immune Tolerance Induction (Not Applicable for PA8 EEA/UK v1)

- Primary:
  - The success rate of ITI therapy with BAX 855.
- Secondary:
  - The rate of partial success and failure of ITI with BAX 855.
  - ABR during ITI.
  - Weight-adjusted consumption of BAX 855 per month and per year for each ITI regimen employed.
  - Catheter-related complications.
  - Binding IgG and IgM antibodies to FVIII, PEG-FVIII, and PEG.

3.3 Exploratory Outcomes Measure

[redacted]

[redacted]

4. ANALYSIS SETS

4.1 All Subjects Enrolled Set (ENR)

The all subjects enrolled set (ENR) is to contain all subjects for whom informed consent has been provided.

Informed consent information 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. If a subject receives BAX 855 (commercial Adynovate/Adynovi) during screening period or at screening, the subject is to be included in the SAS even if the subject is a screen failure. All safety analyses for BAX 855 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
- *FVIII Activity Infusion for Determination of Incremental Recovery* eCRF panel

In addition, as a subset of the safety analysis set (SAS), the Long Term Safety Analysis Set (LTSAS) is defined as subjects completing at least 5 years of study treatment.

4.3 Prophylaxis Analysis Set (PAS)

The prophylaxis analysis set (PAS) is to comprise all subjects included in the SAS and have been treated with prophylaxis regimen.

Information on subject regimen is to be obtained from the *Confirmation of Eligibility* and *Change of Dose* eCRF panels.

4.4 Hemostatic Efficacy Analysis Set (HEAS)

The hemostatic efficacy analysis set (HEAS) is to comprise all subjects who were treated for one or more bleeds with BAX 855.

Information on treatment of bleeds with BAX 855 is to be obtained from the *Bleeding Episode* eCRF panels where type of treatment is BAX 855.

4.5 Pharmacokinetic Analysis Set (PKAS)

The PK analysis set (PKAS) is to comprise all subjects in the SAS who have at least one post-dose measurement of FVIII activity without protocol deviations and/or events with potential to affect concentration (FVIII activity levels). The PK scientist is to evaluate the strategy for dealing with data affected by protocol deviations before any analysis is performed.

4.6 FVIII Inhibitor Detection Analysis Set (IDAS)

The FVIII inhibitor detection analysis set (IDAS) is to comprise all subjects who developed confirmed inhibitors to FVIII.

A subject is considered to have developed confirmed FVIII inhibitors when the subject has FVIII result from central laboratory ≥ 0.6 BU confirmed by a second repeat blood sample of ≥ 0.6 BU drawn within 2 weeks of site notification of an inhibitor.

4.7 FVIII Inhibitor Enrolled Analysis Set (IEAS)

The FVIII inhibitor enrolled analysis set (IEAS) is to comprise all subjects in the IDAS who indicated that they have moved to FVIII inhibitor treatment part of the study. FVIII inhibitor treatment screen failure subjects are to be included.

Information on whether a subject moved to FVIII inhibitor treatment part of the study is to be obtained from the *Patient Status* eCRF panels.

4.8 FVIII Inhibitor Treatment Analysis Set (IAS)

The FVIII inhibitor treatment analysis set (IAS) is to comprise all subjects that received at least one FVIII inhibitor treatment with BAX 855 during the study after the date that subject moved to FVIII inhibitor treatment.

Whether subject moved to FVIII inhibitor treatment and the date that the subject moved to FVIII inhibitor treatment is to be obtained from *Patient Status* eCRF panels. The information on FVIII inhibitor treatment with BAX 855 is to be obtained from the *Study Infusion* eCRF panels.

Subjects that move to FVIII inhibitor treatment based on results of the local laboratory and FVIII inhibitor is not confirmed by central laboratory second repeat blood sample, and transitions back to main study due to inhibitors that are not confirmed by central laboratory, are to be included in the IAS but not in the IDAS.

Subjects that developed inhibitors that are confirmed by second repeat blood sample from central laboratory, but do not move to FVIII inhibitor treatment and stay in main study, are to be included in the IDAS but not in the IAS.

4.9 Invasive Procedure Analysis Set (IPRAS)

The invasive procedure analysis set (IPRAS) is to comprise all subjects who were treated with BAX 855 for one or more surgeries or invasive procedures in the context of the study.

Information on treatment of surgeries with BAX 855 is to be obtained from the *Study Infusion Invasive Procedure* and *Study Infusion Surgery* eCRF panels.

5. STATISTICAL CONSIDERATIONS

5.1 Interim Analyses

An interim analysis is to be performed once 50 subjects have accumulated at least 50 EDs to BAX 855 or have developed a confirmed inhibitor to FVIII for regulatory purposes and is to comprise the same analyses planned for the final analysis as set out in this document. All data up to the date that 50 subjects reach 50 EDs or have developed a

confirmed inhibitor to FVIII is to be cleaned and presented in the outputs. Biostatistics is to take a snapshot of all the data for the outputs up to this date except for development of a confirmed FVIII inhibitor which must be included in the analysis even if it occurred after the cut-off.

5.2 Final Analyses

All final planned analyses identified in this SAP are to be performed by IQVIA Biostatistics following Takeda's authorization of this SAP and Database Lock. The final analysis is to be performed on a clean database.

5.3 Reference Start Date, Study Day, Inhibitor Detection Day and Inhibitor Treatment Day

5.3.1 Reference Start Date and Study Day

The reference start date is defined as the day of the first BAX 855 infusion. If a subject receives a BAX 855 (or commercial Adynovate/Adynovi) infusion before or during screening, this is to be used as the reference start date. The reference start date is to be referred to as Study Day 1. Subjects that discontinue study participation prior to receiving any BAX 855 dose, are not to have a reference start date.

Study day is to be calculated as described below from the reference start date 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 start date, then:

$$Study\ \ Day = (Date\ of\ Event - Reference\ \text{Start}\ Date) + 1.$$

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

$$Study\ Day = (Date\ of\ Event - Reference\ \text{Start}\ Date).$$

Partial or missing assessment/event dates are not expected, except for AEs and concomitant medications. In case the assessment/event date is partial or missing, study day and corresponding durations are not to be calculated and "not available" is to be displayed in the output.

5.3.2 Inhibitor Detection Day

Inhibitor detection date is calculated for subjects who developed inhibitors to FVIII confirmed by central laboratory with a second blood sample and is defined as the date on which the first inhibitor to FVIII was detected. Inhibitor detection date is to be referred to as Inhibitor Detection Day 1. Subjects whose inhibitors to FVIII were not confirmed by the second blood sample from the central lab are not to have an inhibitor detection date.

Inhibitor detection day is to be calculated as described below from the inhibitor detection date:

$$Inhibitor\ Detection\ Day = (Date\ of\ Event - Inhibitor\ Detection\ \text{Start}\ Date) + 1.$$

5.3.3 Inhibitor Treatment Day

Inhibitor treatment start date is calculated for subjects who received at least one BAX 855 infusion after the date that the subject moved to FVIII inhibitor treatment. Inhibitor treatment start date is defined as the date on which the subject receives first BAX 855 infusion after the date that the subject moved to FVIII inhibitor treatment. Inhibitor treatment start date is to be referred to as Inhibitor Treatment Day 1. Subjects that do not receive any FVIII inhibitor treatment are not to have an inhibitor treatment start date. Inhibitor treatment day is only to be displayed for events that took place after the subject moved to FVIII inhibitor treatment.

Inhibitor treatment day is to be calculated as described below from the inhibitor treatment start date:

$$Inhibitor\ Treatment\ Day = (Date\ of\ Event - Inhibitor\ Treatment\ Start\ Date) + 1.$$

5.4 Handling of Missing, Unused, and Spurious Data

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

For PK data, if any concentration data are considered spurious (e.g. lack of biological plausibility), the reason for exclusion and the analysis from which the data point is to be excluded are to be documented.

Exposure:

Should body weight (as obtained from *Vital Signs* eCRF panels) be missing for a subject at time of study infusion, linear interpolation of the available body weight measurements is to be performed to compute weight-adjusted BAX 855 consumption.

Adverse Event:

- Handling of unknown causality assessment:
  - If a subject experiences an AE with a missing causality assessment, the relationship of the AE is to be counted 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", the severity of this 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", the severity of this AE is to be counted as "unknown".
- Handling of missing or partial AE starting date:
  - If AE starting date is completely missing, an AE will be considered to have AE occurred on or after BAX 855 administration date.
  - For AE with partial date, the following will be considered as AE occurred on or after BAX 855 administration.
    - If only year and month of AE onset is available, compare years and months between AE starting date and first dose date, and, year and month of AE onset is the same or after year and month of first dose date.
    - If only year of AE onset is available, compare year between AE starting date and first dose date, and, year of AE onset is the same or after year of first dose date.

The presentation of missing data in output is to be presented as set out in the latest version of the Output Templates.

5.5 Definition of Baseline

Unless otherwise specified, 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, Study Day, Inhibitor Detection Day and Inhibitor Treatment Day. In the case where the last non-missing assessment and the reference start date coincide, the assessment is to be considered pre-baseline.

If a subject received BAX 855 (commercial Adynovate/Adynovi) before screening the subject will not have any baseline results. If a subject receives BAX 855 during screening period, baseline is still defined as the last non-missing (scheduled or unscheduled) measurement obtained prior to the reference start date.

5.6 Definition of Visit Windows

All data are to be presented by nominal visit as recorded in the eCRF. Visits are not to be reassigned from the recorded nominal visit to any other visit based on dates. Data management is to check where visit schedule is followed as indicated below.

Subjects are to complete study visits as follows: Baseline Visit, Visits 1 to 3 after every 5 ± 1 EDs until 20±2 EDs at Visit 4, Visits 5 and 6 after every 10 ± 3 EDs, Visit 7 at 50-55 EDs, Visit 8 at 75 ± 5 EDs; and the Study Completion/Termination Visit for follow-up at 100-110 EDs.

If there is a situation in which a prolonged treatment of a bleed results in a cumulative ED count that exceeds a specific ED-directed visit, the ED-directed visit is to take place at the next non-bleeding infusion, where feasible. For example, a subject with two EDs who requires five EDs to treat a bleed would accumulate seven EDs and miss study Visit 1 (5 ± 1 ED) at the scheduled time. Study Visit 1 is to be completed at ED eight and the subject is to continue with study Visit 2 at the appropriate time (10 ± 1 EDs).

If there is a situation in which two or more ED-directed visits must be missed due to ongoing bleeding treatment, the most recent, omitted visit should be conducted at the first non-bleeding ED, where feasible. For example, a subject with two EDs who requires ten EDs to treat a bleed would accumulate 12 EDs and miss study Visits 1 (5 ± 1 EDs) and 2 (10 ± 1 EDs) at the scheduled times. Study Visit 2 is to be completed at ED 12 and the subject is to continue with study Visit 3 at the appropriate time (15 ± 1 EDs).

Subjects who develop FVIII inhibitors and continue receiving BAX 855 are to complete the following study visits: Visit 1 at Week 2 ± 2 days, Visit 2 at Week 4 ± 2 days, and subsequent visits every month ± 1 week up to 33 months of total inhibitor treatment.

5.7 Changes from the Planned Statistical Analysis in Protocol

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

- The ITI analysis set in PA8 (Global) has been changed to FVIII inhibitor treatment analysis set and is to include subjects with confirmed FVIII inhibitors of PA8 EEA/UK.
- The surgery analysis set in PA8 (Global) has been changed to invasive procedure analysis set to include both subjects under PA8 (Global) who were dosed with at least one BAX 855 infusion during surgery and subjects under PA8 EEA/UK who were dosed with at least one BAX 855 infusion during an invasive procedure.
- An ENR analysis set has been added to include all subjects who were enrolled.
- IDAS has been added to include all subjects who developed confirmed inhibitors to FVIII.
- IEAS has been added to include all subjects who moved to the FVIII inhibitor treatment part of the study, whether they received FVIII inhibitor treatment or not.
- An additional PK analysis set is to be defined to keep only subjects with at least one post-dose measurement of FVIII activity to calculate IR.

5.8 Statistical Tests

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

Unless otherwise specified, the default summary statistics for quantitative variables are to be as follow:

- The number of subjects in each category (n)
- Mean
- Standard deviation (SD)
- First quartile (Q1)
- Median
- Third quartile (Q3)

- Interquartile 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 that are to be made in any presentations.

If the original data have 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
- 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 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:

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

For main study outputs that are to be summarized by year after first BAX 855 exposure, the year after first BAX 855 exposure is calculated with the following formula:

$$Year\ after\ first\ BAX\ 855\ exposure = ceiling\left(\frac{Study\ Day}{365.2425}\right),$$

where ceiling is rounding up to the nearest integer.

For FVIII inhibitor treatment outputs that are to be summarized by year after first BAX 855 exposure, the year after first BAX 855 exposure is to be calculated with the following formula:

$$Year\ after\ first\ BAX\ 855\ exposure = ceiling\left(\frac{Intensified\ Treatment\ Day}{365.2425}\right).$$

Result at baseline visit is to be used for zero years after first BAX 855 exposure. For each year after year zero, the worst result per subject is to be used for qualitative data (binding antibodies to FVIII, PEG-FVIII and PEG and abnormal laboratory and vital signs) and the weighted average for quantitative results (incremental recovery). A result is to be imputed at each year after first BAX 855 exposure.

The interpolated result at each year after first BAX 855 exposure is to be calculated as follows:

$$\frac{x_{i-1} - x_i}{t_{i-1} - t_i} = \frac{x - x_i}{t - t_i},$$

$$x = \frac{(t - t_i)(x_{i-1} - x_i)}{(t_{i-1} - t_i)} + x_i$$

where x_{i-1} is the first available result before the result to be interpolated, x_i is the first available result after the result to be interpolated, t_{i-1} is the duration in months from the baseline visit to the date of the first available result before the result to be interpolated, t_i is the duration in months from the baseline visit to the date of the first available result after the result to be interpolated, x is the interpolated result to be calculated and t is the duration in months from baseline visit to the interpolated result.

Weighted average is to be calculated as follows:

$$Weighted\ average = \frac{\sum_{j=1}^{n} d_j x_j}{\sum_{j=1}^{n} d_j},$$

where d_j is the duration in months from the previous result to a particular result, x_j is the result at a particular timepoint and n is the number of results for a particular year after the first BAX 855 exposure.

5.10 Multicenter Studies

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

Since the number of subjects per center will be low, all summaries are to be produced overall and not 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 *Confirmation of Eligibility, Change of Dose* and *Patient Status* eCRF panels:
  - Main study:
    - On-demand
    - Prophylaxis
  - FVIII inhibitor treatment:
    - 50 IU/kg three times weekly
    - 100-200 IU/kg daily

5.12 Adjustment for Multiplicity

Not applicable.

6. STUDY SUBJECTS

6.1 Disposition of Subjects

All subjects, or their legal representatives, as required, that provide informed consent (i.e., signs and dates the informed consent form and assent form, if applicable) are to be accounted for in this study. When a subject moves to FVIII inhibitor treatment, a PA4 subject is required to have a new informed consent signed, but a PA5 subject is not

required to have a new informed consent signed. An individual subject's participation starts once informed consent has been provided and ends at the completion/termination visit at 100 – 110 EDs or when the subject has a confirmed FVIII inhibitor ≥ 0.6 BU at the central laboratory and does not participate in FVIII inhibitor treatment. For PA5 subjects that develop a confirmed FVIII inhibitor, participation continues until the inhibitor disappears or for 33 months. For PA4 subjects that develop a confirmed FVIII inhibitor, participation for Part B of the study starts once the subject provides informed consent and ends at treatment success, failure or at 33 months.

Subject participation period is approximately two years from enrollment to the subject completion, unless prematurely discontinued. In case of inhibitor development, participation may be extended with up to 33 additional months.

Any subject may voluntarily withdraw consent for continued participation and data collection. The reason for withdrawal is to be recorded in the eCRF.

The following information on subject disposition is to be recorded in the eCRF:

- Date of visit (*Date of Visit* eCRF panel)
- Follow-up visits for FVIII inhibitor treatment subjects (*Follow-up Visit* eCRF panel)
- Date and time of informed consent and protocol version (*Screening* eCRF panel)
- Inclusion and exclusion criteria met and/or not met (*Inclusion/Exclusion Criteria* eCRF panels)
- AE description (*Adverse Events* eCRF panel)
- Date and time of death and the primary cause of death (*Death* eCRF panel)
- Study infusion information (*Study Infusio*n and *FVIII Activity Infusion for Determination of Incremental Recovery* eCRF panels)
- Study surgery infusion information (*Study Infusion Surgery* eCRF panel)
- Study completion (*Completion/Termination* eCRF panels)

The following derivations based on information recorded in the eCRF are to be performed:

- A subject is to be considered enrolled if date of informed consent is present.

- A subject is to be considered as dosed with at least one on-demand BAX 855 infusion if a subject received an infusion to treat a bleeding episode, maintain hemostasis, surgical prophylaxis, invasive procedure or standard of care before a prophylaxis infusion or if subject received only the infusion for determination of IR and no other infusions.
- A subject is to be considered as dosed at least once for the 100-200 IU/kg daily regimen if the subject developed inhibitors to FVIII and the subject moved to "High ITI" as reported in *Patient Status* eCRF panels and received at least one BAX 855 infusion after FVIII inhibitor development.
- A subject is to be considered as dosed at least once for the 50 IU/kg three times weekly regimen if the subject developed inhibitors to FVIII and the subject moved to "Low ITI" as reported in *Patient Status* eCRF panels and received at least one BAX 855 infusion after FVIII inhibitor development.
- A subject is to be considered as dosed with at least one prophylactic BAX 855 infusion if a subject has been treatedwith any BAX 855 prophylactic regimen.
- A subject is to be considered as dosed with at least one inhibitor treatment if a subject received at least one infusion for FVIII inhibitor treatment.
- A subject is to be considered completed if the primary reason for completion/termination is recorded as "Subject completed study".
- Primary reason for termination is to be considered as died if a date of death is available in a subject's *Death* eCRF panel.
- The AE description is to be linked with the primary reason for completion/termination (should the reason be AE related) by linking the AE number reported in the *Completion/Termination* eCRF panel with the AE number in the *Adverse Event* eCRF panel.

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

Planned presentation of listings on the disposition of subjects are to include subject disposition and information on inclusion and exclusion eligibility for the ENR and IEAS, visit dates and analysis sets for the ENR.

6.2 Demographic and Baseline Characteristics

The following information on subject demographics and baseline characteristics is to be recorded in the eCRF:

- Subject demographics (*Demographic* eCRF panel)
- Weight and height at screening and baseline (*Vital Signs* eCRF panel)
- Information on hemophilia A history, blood group and first FVIII injection (*Hemophilia A History/Blood Group/Target Joint Identification/First FVIII injection* eCRF panel)

If gene mutation is not known at screening and is obtained from central laboratory results from external vendor at a later visit, the gene mutation from central laboratory is to be used for demographic, baseline and disease characteristics. If both gene mutation at screening and central laboratory is recorded, then gene mutation from the central laboratory is to be used. Each gene mutation is to be classified as a high or low risk mutation for inhibitor formation by medical.

The following derivations based on information recorded in the eCRF are to be performed:

- If age is specified in months, it is to be converted to years by using the following formula:

$$Age\ in\ years = Age\ in\ months/12.$$

- BMI (body mass index) is to be calculated as:

$$BMI(kg/m^2) = weight(kg)/[height(m)]^2.$$

- Height in cm is to be converted to m using the following formula:

$$Height[m] = \frac{Height[cm]}{100}.$$

- Race is to be presented as "Multiple" in summaries if more than one race is selected on the eCRF panel.

Tables on demographic and baseline characteristics are presented for the SAS, PKAS, PAS, HEAS, IDAS, IEAS, IAS and IPRAS. The baseline demographics and disease characteristics are to include age at informed consent [years], weight at screening [kg], height at screening [cm], body mass index at screening [kg/m^2], weight at baseline [kg], height at baseline [cm], body mass index at baseline [kg/m^2], FVIII at screening [BU], exposure days prior to screening, CD4+ count at screening [%], platelet count at screening [10^9/L], ALT at screening [U/L], AST at screening [U/L] and serum creatinine at screening [µmol/L].

Planned presentation of listings on demographic and baseline characteristics are to include baseline demographics and disease characteristics at screening for the SAS.

6.3 Medical History

Information on medical history is to be recorded in the eCRF (*Medical History* eCRF panel).

Information on medical histories and surgeries is to be listed and summarized for the SAS.

6.4 Prior PEGylated Medication History

Information on prior PEGylated medication history is to be recorded in the eCRF (*Prior Pegylated Medication History* eCRF panel).

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

6.5 Concomitant Medications and Non-Drug Therapies

The following information on concomitant medications and non-drug therapies is to be recorded in the eCRF:

- Concomitant medications, non-drug therapies and procedures (*Concomitant Medication/Non-Drug Therapy* eCRF panel)
- AE description (*Adverse Events* eCRF panel)
- Medical history description (*Medical History* eCRF panel)

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

The following derivations based on information recorded in the eCRF are to be performed:

- Assignment to Prior or Concomitant:

- A medication, non-drug therapy or procedure is to be assigned as "Prior" if the medication or non-drug therapy stopped prior to first BAX 855 administration.
- A medication, non-drug therapy or procedure is to be assigned as "Concomitant" if the medication or non-drug therapy:
  - Started after first BAX 855 administration or
  - Started before the first BAX 855 administration and ended after first BAX 855 administration or is still ongoing.
- A medication, non-drug therapy or procedure is to be assigned as "Unknown" if missing dates do not allow for assignments based on above rules.

- The AE description is to be linked with the reason for medication (should the reason be AE related) by linking the AE number reported in the *Concomitant Medication/Non-Drug Therapy* eCRF panel with the AE number in the *Adverse Event* eCRF panel.
- The Medical History description is to be linked with the reason for medication (should the reason be medical history related) by linking the medical history number reported in the *Concomitant Medication/Non-Drug Therapy* eCRF panel with the medical history number in the *Medical History* eCRF panel.

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

6.6 Extent of Exposure

The following information on infusions is to be recorded in the eCRF:

- Study infusions information (*Study Infusion* and *FVIII Activity Infusion for Determination of Incremental Recovery* eCRF panels)
- Regimen information (*Confirmation of Eligibility* eCRF panels and *Patient Status* eCRF panels)
- Planned dose information (*Confirmation of Eligibility* eCRF panels)
- Change of dose information (*Change of Dose* eCRF panel)
- Determination and confirmation of FVIII inhibitors (*Determination / Confirmation of FVIII Inhibitors* eCRF panel)
- Treatment with by-passing agents (*By Passing Agent treatment* eCRF panels)
- FVIII by-passing agents information (*By-Passing agents* eCRF panel)

- Body weight (*Vital Signs* eCRF panels)

The following derivations based on information recorded in the eCRF are to be performed:

- Weight adjusted dose is to be calculated using the following formula:

$$Weight\ adjusted\ dose\ [IU/kg] = \frac{Total\ Units\ Infused\ [IU]}{Body\ Weight\ [kg]},$$

  refer to Section 5.4: Handling of Missing, Unused, and Spurious Data for definition of body weight.
- Prophylactic infusions for subjects in the main study are to be divided between prophylactic infusion < 50 IU/kg and prophylactic infusion ≥ 50 IU/kg.
- All infusion information obtained from the *FVIII Activity Infusion for Determination of Incremental Recovery* eCRF panel, is to have reason for infusion as "Incremental Recovery".
- A subject that has not developed inhibitors to FVIII is to be included in the on-demand regimen, until the subject moves to the next regimen, if the question "Planned Dosing Regimen" is indicated as "On-Demand" on the *Confirmation of Eligibility* eCRF panels. A subject is included in the prophylaxis regimen if question "Planned Dosing Regimen" is indicated as "Prophylaxis" on the *Confirmation of Eligibility* eCRF panels or if the question "Reason for Change" is indicated as "Transitioned to Prophylactic Regimen" on the *Change of Dose* eCRF panel.
- A subject that has developed inhibitors to FVIII is to be included in the 100-200 IU/kg daily regimen if the question "Subject moving to?" is indicated as "High ITI" on the *Patient Status* eCRF panels and a subject is included in the 50 IU/kg three times weekly regimen if the question "Subject moving to?" is indicated as "Low ITI".
- 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 as one ED. EDs is to be determined overall and by reason for infusion (prophylaxis, bleeding episodes, to maintain hemostasis, incremental recovery, FVIII inhibitor treatment, invasive procedures).
- EDs until confirmed inhibitor development (confirmed with the second repeated blood sample within 2 weeks of the first blood sample) are the number of EDs from the start of the study until development of confirmed FVIII inhibitor (1st

positive date) as obtained from *Determination / Confirmation of FVIII Inhibitors* eCRF panel.

- EDs and EDs until confirmed inhibitor development are to be categorized as follows:

  For subjects in the main study and subjects undergoing invasive procedures the following categories are to be used:

  - < 10 EDs
  - 10 to < 20 EDs
  - 20 to < 30 EDs
  - 30 to < 40 EDs
  - 40 to < 50 EDs
  - 50 to < 75 EDs
  - 75 to < 100 EDs
  - ≥ 100 EDs

  For subjects undergoing FVIII inhibitor treatment the following categories are to be used:

  - < 50 EDs
  - 50 to < 100 EDs
  - ≥ 100 EDs

- Total number of infusions is determined as the count of the number of infusions, regardless of date and time, the subject had. Number of infusions is to be determined overall and by reason for infusion (prophylaxis, bleeding episodes, to maintain hemostasis, incremental recovery, FVIII inhibitor treatment, invasive procedures).
- Total dose (IU/kg or IU as applicable) is to be calculated by the sum of all doses, overall and by reasons for infusion, during the observation period.
- The average number of infusions per infusion reason (bleeding episode and to maintain hemostasis) is to be calculated using the following formula:

$$Average\ number\ of\ infusions = \frac{Total\ number\ of\ infusions\ for\ reason}{Number\ of\ occurrences\ of\ reason}.$$

- The average number of infusions per time period (weeks, months, years) is to be calculated as the total number of infusions during the observation period, divided

by the duration for the particular time period (weeks, months, years). This is applicable for prophylaxis and FVIII inhibitor treatment.

- The average dose per reason (prophylactic, bleeding episodes, maintain hemostasis, FVIII inhibitor treatment and invasive procedure) is to be calculated using the following formula:

$$Average\ dose\ [IU/kg] = \frac{Total\ dose\ [\text{IU/kg}]\ for\ reason}{Number\ of\ infusions\ for\ reason}.$$

- The average dose per time period (weeks, months, years) is to be calculated by the total dose (IU/kg or IU as applicable) the subject received during the observation period, divided by the duration for the particular time period (weeks, months, years). This is applicable for prophylaxis and FVIII inhibitor treatment.
- The observation period for efficacy (OPE) by regimen (on-demand, prophylaxis and FVIII inhibitor treatment) in days for each subject, is to be calculated using the following formula:
    - If a subject had no invasive procedures:
      $OPE\ [days] = Regimen\ Stop\ Date - Regimen\ Start\ Date + 1,$
    - If a subject had at least one invasive procedure:
      $OPE\ [days] = Regimen\ Stop\ Date - Regimen\ Start\ Date + 1 - Duration\ in\ Surgery\ in\ Regimen,$

  where "Regimen Start Date" refers to the date of first BAX 855 infusion in the study regimen. "Regimen Stop Date" refers to either:
    - date that subject started in next regimen minus one day or
    - minimum between completion/termination date and date of last BAX 855 infusion in regimen plus infusion frequency if subject completed/terminated the study in regimen or
    - if subject discontinued study in on-demand regimen, "Regimen Stop Date" is to be termination date.

  "Duration in invasive procedure" refers to the total number of days that the subject was in invasive procedures (difference between the discharge date and invasive procedure start date in days) during specific regimen.

- The observation period for efficacy (OPE) by study part (main study, FVIII inhibitor treatment or overall) in days for each subject, is to be calculated using the following formula:
    - If a subject had no invasive procedure:
    $$OPE\ [days] = Study\ Stop\ Date - Study\ Start\ Date + 1,$$
    - If a subject had at least one invasive procedure:
    $$OPE\ [days] = Study\ Stop\ Date - Study\ Start\ Date + 1 - Duration\ in\ Surgery\ in\ Study\ Part,$$

  where "Study Start Date" refers to the date of first BAX 855 infusion in the study part and "Study Stop Date" to either:
    - date that subject started in next study part minus one day or
    - minimum between completion/termination date and date of last BAX 855 infusion in study part plus infusion frequency if subject completed/terminated the study in study part.
- The OPE in weeks is to be calculated using the following formula:
$$OPE\ [weeks] = \frac{OPE\ [days]}{7}.$$
- The OPE in months is to be calculated using the following formula:
$$OPE\ [months] = \frac{OPE\ [days]}{365.2425} \times 12.$$
- The OPE in years is to be calculated using the following formula:
$$OPE\ [years] = \frac{OPE\ [days]}{365.2425}.$$

For data integration purposes, 30 subjects on PA2 or PA3 were assigned to complete *Study Infusion* eCRF panel for original protocol instead of PA2 or PA3. There is no difference between *Study Infusion* eCRF panel for original protocol and *Study Infusion* eCRF panel for PA3. The only difference between *Study Infusion* eCRF panel for original protocol and *Study Infusion* eCRF panel for PA2 is surgical prophylaxis as a reason for infusion on original protocol which is not on PA2. It was decided to keep the subject data with the original protocol since the difference was minor and there was risk in losing data information if moved to PA2 or PA3.

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

6.7 Measurements of Treatment Compliance

Treatment compliance is to be derived using results and derivations obtained from study exposure as described in Section 6.6: Extent of Exposure.

Treatment compliance is to be based on the following:

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

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

- Time since last infusion on the "prophylaxis regimen":
  - Does not exceed 8 days if dose frequency is once a week
  - Does not exceed 5 days if dose frequency is twice a week
  - Does not exceed 4 days if dose frequency is three times a week.
- Time since last infusion on the "100 – 200 IU/kg daily regimen" does not exceed 36 hours (or 1 day where time is not available).
- Time since last infusion on the "50 IU/kg three times weekly regimen" does not exceed 4 days.

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

$$Time\ not\ Covered\ [Days]\ = \\ Days\ since\ last\ BAX\ 855\ infusion - Treatment\ regimen\ allowed\ days$$

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

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

$$Time\ Covered\ [\%] = \frac{OPE[Days] - Total\ Time\ not\ Covered\ [Days]}{OPE[Days]} \times 100$$

An infusion is considered in adherence to the recommended prophylactic dose if the actual amount infused (IU/kg) is 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.

Treatment compliance is to be summarized for the SAS, and IAS and listed for the SAS. Summaries are to be presented by treatment regimen at time of dose for SAS and IAS.

6.8 Protocol Deviations

Protocol deviations are to be listed and summarized for the ENR and IEAS as obtained from the Clinical Trial Management System (CTMS). Protocol deviations from the CTMS are to be coded to categories and provided as part of the CTMS transfer to Biostatistics. These categories are:

- Informed consent
- Eligibility and entry criteria
- Concomitant medication criteria
- Laboratory assessment criteria
- Study procedures criteria
- Serious AE criteria
- Randomization criteria
- Visit schedule criteria
- IP compliance
- Efficacy criteria
- Administrative criteria
- Source document criteria
- Regulatory or Ethics approvals criteria
- Other criteria

Changes to the procedures or events, which may impact the quality of the PK data, are to be considered significant protocol deviations and are to be described within the clinical study report body text. These changes or events are to include any circumstances that are to alter the evaluation of the PK. An example is, but may not be limited to, inaccurate

dosing on the day of PK sampling. In the case of a significant protocol deviation or event with the potential to affect PK, PK data collected are to be excluded from the PK analysis and descriptive statistics. Other changes to the procedures or events which do not impact the quality of the PK data are not to be considered significant protocol deviations. A common example of a non-significant protocol deviation is a missed blood sample or deviations from blood collection times.

7. EFFICACY EVALUATION

7.1 Bleeding Episodes

Efficacy outcomes as described in this section form part of the secondary objective of the study.

The following information on bleeding episodes is to be recorded in the eCRF:

- Bleeding episodes (*Bleeding Episode* eCRF panels)
- History of bleeding episodes (*History of bleeding episode* eCRF panel)
- Bleeding during screening period (*Bleeding during screening period* eCRF panel)
- Infusion information (*Study Infusion* eCRF panels and *FVIII Activity Sampling for Determination of Incremental Recovery* eCRF panel)
- New target joints (*Development of New Target Joints* eCRF panel)
- Ultrasound (*Ultra Sound* eCRF panel)

The following derivations based on information recorded in the eCRF are to be performed:

- The following anatomical bleeding sites are considered 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 confirmed by medical as a joint. Medical is to review all free text to determine whether the site is considered a joint.
- A joint is noted as a target joint if a single joint (ankles, knees, hip or elbow) has ≥3 spontaneous bleeding episodes in any consecutive six-month period.
- A joint will cease to be considered as a target joint if identified in the eCRF with ≤2 bleeds into the joint within a consecutive twelve-month period.
- A bleeding site is noted as a target joint if the specific joint is considered a target joint at the time of the bleed.
- A bleeding site is noted as a treated target joint if the specific joint is considered a target joint at the time of the bleed and required treatment. If no treatment was required, the target joint is noted as a non-treated target joint.
- A bleeding site is noted as a non-target joint if the specific joint is not considered a target joint at the time of the bleed. The bleeding site must be a joint to be noted as a non-target joint.
- A bleed is noted as an injury related bleed if the cause of the bleed is indicated as "Injury".
- A bleed is noted as a spontaneous bleed if the cause of bleed is indicated as "Spontaneous".
- A bleed is noted as a bleed of unknown causality if the cause of bleed is indicated as "Unknown".
- A bleed is noted as a major bleed if the severity is indicated as "Major".
- A bleed is noted as a moderate bleed if the severity is indicated as "Moderate".
- A bleed is noted as a minor bleed if the severity is indicated as "Minor".
- A bleed is noted as a weekday bleed if the bleed started on a Monday, Tuesday, Wednesday, Thursday or Friday.
- A bleed is noted as a weekend bleed if the bleed started on a Saturday or Sunday.
- A bleed is noted as a morning bleed if the bleed started between 04:00 and 11:59.
- A bleed is noted as an afternoon bleed if the bleed started between 12:00 and 17:59.
- A bleed is noted as an evening bleed if the bleed started between 18:00 and 03:59.

- Infusions related to a bleeding episode are to be obtained from the *Study Infusion* eCRF panels, using the bleeding episode number recorded in that form to match with the bleeding episode number in the *Bleeding Episode* eCRF panel.
- Time since last BAX 855 infusion in hours is to be derived as:

$$Time\ (hours) = Date, time\ of\ bleeding\ episode\ onset - Date, time\ of\ last\ BAX\ 855\ dose,$$

where last BAX 855 dose refers to the last infusion received before the bleeding episode.
- Time since last BAX 855 infusion in days is to be derived as:

$$Time\ (days) = Date\ of\ bleeding\ episode\ onset - Date\ of\ last\ BAX\ 855\ dose + 1,$$

where last BAX 855 dose refers to the last infusion received before the bleeding episode.
- If the time since last BAX 855 infusion is less than 24 hours, then the duration is to be displayed in hours. If time since last BAX 855 infusion is greater or equal to 24 hours or time is missing, then the duration is to be displayed in days.
- A bleed is considered to be treated with BAX 855 if any infusion of BAX 855 was given after onset of the bleed and before the bleed was controlled.
- The number of bleeds per subject overall and by location (target joint, non-target joint and non-joint), causality (spontaneous, unknown and injury-related) and severity (mild, moderate and severe) is to be determined as the count of unique bleeds in each category a subject had during the observation period.

- Annualized bleeding rate (ABR) includes both treated and non-treated bleeding episodes and is to be derived on the subject-level as:

$$ABR = \frac{Number\ of\ unique\ bleeds}{OPE\ (years)}.$$

The ABR is to be calculated for overall, less than 6 months, and 12 months or longer of the study treatment to be analyzed over the set of subjects using a generalized linear mixed model fitting a negative binomial distribution with logarithmic link function. Different models are to be fitted for main study and FVIII inhibitor treatment regimens and are to include the treatment regimen at time of bleed (on-demand or prophylaxis for the main study and 50 IU/kg three times weekly or 100-200 IU/kg daily for FVIII inhibitors) as a covariate and the natural logarithm of the OPE in years as an offset.

In addition, the ABR during the main study will be analyzed similarly for the following treatment regimens:

- On-demand
- Prophylaxis once per week
- Prophylaxis more than once per week

The following SAS® (SAS Institute Inc, 2017) code similar to the code shown below can be used to perform the analysis and may be modified based on …:

```
PROC GLIMMIX DATA = <ds>;
  CLASS <regimen> <usubjid>;
  MODEL <bleeds> = <regimen> / DIST = NEGBIN OFFSET = <log_OPE>
  LINK = LOG;
  RANDOM _residual_ / SUB = <usubjid> group=<regimen> Type=CS CL;
  LSMEANS <regimen> / BYLEVEL OM CL;
  ODS OUTPUT LSMEANS = <outds>;
RUN;
QUIT;
```

where <ds> refers to the input dataset, <regimen> the treatment regimen at time of bleed, <bleeds> the number of bleeds during the observation period, <log_OPE> the natural logarithm of the OPE in years and <usubjid> the unique subject identifier. Point estimates and confidence intervals obtained from the generalized linear mixed model are to be anti-logged prior to presentation.

In the event that the GLIMMIX procedure fails to converge, appropriate steps are to be taken to investigate possible root causes to determine if any adjustments are plausible.

The model results are to be presented on the SAS and IAS for:

- The total ABR
- Annualized joint bleeding rate
- Annualized non-joint bleeding rate
- Annualized target joint bleeding rate
- Annualized treated target joint bleeding rate
- Annualized non-target joint bleeding rate
- Annualized non-treated target joint bleeding rate
- Annualized injury related bleeding rate
- Annualized spontaneous bleeding rate
- Annualized unknown causality bleeding rate
- Annualized spontaneous/ unknown causality bleeding rate
- Annualized major 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 evening bleeding rate

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

ABRs for the above categories are to be presented descriptively for the SAS and IAS. Weighted mean, SD, median and quartiles are to be presented using the SAS® (SAS Institute Inc, 2017) UNIVARIATE procedure. Weights are to be proportional to the observation time of subjects to resemble the mixed model analyses. Descriptive statistics on outcome and characteristics of bleeding episodes are to be presented for the SAS and IAS. Summaries for bleeding episodes are to be presented by treatment regimen at time of bleed. Presentation of the number of infusions to treat a bleed is to include the 95% confidence interval. The 95% confidence interval on the median will be determined using

the distribution-free confidence interval for the 50th percentile from the SAS® (SAS Institute Inc, 2017) UNIVARIATE procedure.

For bleeds treated with BAX 855, the efficacy rating at 24 hours after first infusion, the efficacy rating at bleed resolution, the PI's (principal investigator's) assessment at 24 hours after first infusion and the PI's assessment at bleed resolution are to be summarized for the SAS.

Information on bleeding episodes before and during screening is to be listed for the ENR. Information on bleeding episodes during the study is to be listed for the SAS and IAS and the course of target joints and ultrasound information is to be listed for the SAS.

7.2 Invasive Procedures

Invasive procedures are not applicable to confirmed FVIII inhibitor treatment subjects. Efficacy of BAX 855 for perioperative management is part of the secondary objective of the study. Invasive procedures are to include surgeries.

The following information on invasive procedures is to be recorded in the eCRF:

- Planned invasive procedures (*Planned Surgery*, *Invasive procedure* and *Surgery* eCRF panels)
- Invasive procedures report (*Surgical Report* and *Surgical Report – Surgery* eCRF panels)
- Postoperative efficacy assessment (*Postoperative Efficacy Assessment Scale* eCRF panel)
- Perioperative efficacy assessment (*Perioperative Efficacy Assessment Scale* eCRF panel)
- Intraoperative efficacy assessment (*Intraoperative Efficacy Assessment* eCRF panel)
- Estimated Blood Loss (*Estimated Blood Loss* eCRF panel)
- Transfusion Requirements (*Transfusion Requirements* eCRF panel)
- Hemostatic Efficacy Assessment Information (*Intra-operative Global Hemostatic Efficacy Assessment*, *Post-operative Day 1 Global Hemostatic Efficacy Assessment* and *Perioperative Hemostatic Efficacy Assessment* eCRF panels)
- Drain removal blood loss (*Post-Operative 24 Hours / Drain Removal Blood Loss* and *Daily / Drain Removal Blood Loss* eCRF panels)

- Local Laboratory Loading Dose and IP Administration (*Local Laboratory Loading Dose*, *Local Laboratory Supplementary/Rebolus Loading Dose* and *Local Laboratory IP Administration* eCRF panel)
- Central Laboratory IP Administration (*Central Laboratory IP Administration* and *Central Laboratory IP Administration Supplementary/Rebolus* eCRF panels)
- FVIII Peak and Trough Level (*Pre-operative FVIII Peak and Trough level*, *Discharge FVIII Peak and Trough level* and *Post-operative FVIII Peak and Trough level* eCRF panels)

The following derivations based on information recorded in the eCRF are to be performed:

- Grouped overall hemostatic efficacy rating is to be derived as:
  - "Excellent/Good" if overall primary efficacy rating is either "Excellent" or "Good"
  - "Moderate/None" if overall primary efficacy rating is either "Moderate" or "None"
- Grouped actual vs predicted blood loss rating is to be derived as:
  - "Excellent/Good" if grouped actual vs predicted blood loss rating is either "Excellent" or "Good"
  - "Moderate/None" if grouped actual vs predicted blood loss rating is either "Moderate" or "None"

Summary tables containing descriptive statistics will be presented for invasive procedure related blood loss (estimated and observed), hemostatic efficacy (global hemostatic efficacy rating including overall primary hemostatic efficacy rating) and transfusion requirements using the IPRAS.

Subject listings will be presented for the following invasive procedures related items using the IPRAS:

- Planned invasive procedure
- Invasive procedure
- Invasive procedure report
- Estimated blood loss
- Transfusion requirements

- Global hemostatic efficacy assessment
- Drain removal blood loss
- Local laboratory loading dose and IP administration
- Central laboratory IP administration
- FVIII peak and trough level

8. SAFETY EVALUATION

8.1 Adverse Events

The following information on AEs is to be recorded in the eCRF:

- AEs (*Adverse Event* eCRF panel)
- Date and time of BAX 855 administration (*Study Infusions* and *FVIII Activity Infusion for Determination of Incremental Recovery* eCRF panels)
- Reason for not completing the study (*Completion/Termination* eCRF panels)
- Subject demographics (*Demographics* eCRF panel)
- Death (*Death* eCRF panel)
- Concomitant medication (*Concomitant Medication/Non-Drug Therapy* eCRF panel)

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 information recorded in the eCRF 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 of first BAX 855 administration
    - The eCRF question “When did event occur?” has a response of any one of the following:
        - During treatment
        - Within 24 hours after last treatment
        - After more than 24 hours from last treatment

  - If AE start date and eCRF question "When did event occur?" are completely missing
- AEs are considered to have occurred before BAX 855 administration if:
  - The known start date and/or time of the AE is before the date of first BAX 855 administration
  - The eCRF question "When did event occur?" has a response of "Before first treatment with investigational product"
- Duration of AE in hours is to be calculated using the following formula:

$$Duration\ [hours] = AE\ end\ date\ and\ time - AE\ start\ date\ and\ time.$$

- Duration of AE in days is to be calculated using the following formula:

$$Duration\ [days] = AE\ end\ date - AE\ start\ date + 1.$$

- Time since last treatment in hours is to be calculated using the following formula:

$$Time\ since\ last\ treatment\ [hours] = AE\ start\ date\ and\ time - Date\ and\ time\ of\ last\ BAX\ 855\ infusion.$$

- Time since last treatment in days is to be calculated using the following formula:

$$Time\ since\ last\ treatment\ [days] = AE\ start\ date - Date\ of\ last\ BAX\ 855\ dose + 1.$$

- Time since last treatment is only to be calculated 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
- 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", "Probably related" or missing 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 deems 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 the relationship of AE to study medication from a Sponsor perspective.

- Any AE with the question "Action taken on BAX 855" answered as "Drug withdrawn" is to be considered as an AE leading to discontinuation of BAX 855.
- Any AE with primary reason for completion/termination of study to be subject had AE(s) is to be considered as an AE leading to discontinuation of the study. AEs from the *Adverse Event* eCRF panel and *Completion/Termination* eCRF panel are to be linked using the AE numbers recorded on each form.
- 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". The *Adverse Event* and *Death* eCRF panels are to be linked via subject number where event resulted in death.
- An AE is considered related to study procedure if the question "Was event due to study procedure" is indicated as "Yes".
- An AE is considered a thrombotic event if the question "Is this a thrombotic event" is indicated as "Yes" in the eCRF.
- An AE is considered a catheter related AE if the question "Is this event considered to be a catheter related complication" is indicated as "Yes" in the eCRF.

AEs that occurred during or after treatment administration are to be presented in summary tables (for the SAS and IAS respectively). Summary tables are to indicate the number of subjects who experienced AEs as well as the number of AEs. In addition, tables are to be prepared, presenting the number of subjects who experienced an AE at least once and the number of AEs by system organ class and preferred term. AEs are to be summarized by seriousness, severity grades and relationship to the treatment as well.

In addition, AEs including renal, hepatic and neurological events, thromboembolic events, hypersensitivity reactions, inhibitor development, treatment related AEs, serious adverse events (SAEs) will be summarized and listed for subjects with the study treatment for 5 years or more (LTSAS).

All AEs for each subject are to be listed for the SAS and IAS where applicable.

8.2 Clinical Laboratory Evaluations

Results from the central laboratory are to be included in the reporting of this study. Refer to Table 4 and Table 6 in PA5 or Table 7 and Table 9 in PA4 for more information on the

schedule of study procedures and assessments. Laboratory parameters are to be presented using the CDISC compliant terms and standard international (SI) units.

The following information on clinical laboratory evaluations is to be recorded in the eCRF:

- Central laboratory information (*Central Lab Collection* eCRF panel)
- Local laboratory results (*Local Laboratory* eCRF panel)
- Activated partial thromboplastin time (*Activated partial thromboplastin time* eCRF panel)
- AE description (*Adverse Events* eCRF panel)
- MH description (*Medical History* eCRF panel)

The actual laboratory results are to be obtained from an external vendor.

The following derivations based on information recorded in the eCRF are to be performed:

- A result is 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 laboratory result is to be considered as abnormal if the question "Are there any abnormal lab values" is indicated as "Yes".
- A result is to be considered as clinically significant if indicated as such by the Investigator on the eCRF.
- AE term is to be obtained from the *Adverse Events* eCRF panel by merging with the AE number obtained from the applicable eCRF panel.
- MH term is to be obtained from the Medical History eCRF panel by merging with the MH number obtained from the applicable eCRF panel.
- Quantitative laboratory measurements reported as "<X", i.e., below the limit of quantitation (BLQ) are to be presented in listings and figures as "<X", that is, the listings and figures are to present the reported values as is. Presentation of figures are to use the mapped values for plotting purposes but are to present the reported values for labeling purposes.
- Table 1 illustrates the handling of current quantitative laboratory results identified for presentation in tables and figures. The 'mapping' column indicates how analysis values are to be used in tables (if it is to be mapped or not) and how

character analysis values are to be used in listings and figures. In the event that other results are identified during the course of the study, Table 1 examples are to act as a guide for handling of such results or the Sponsor is to be consulted to ensure results are summarized/listed appropriately.

Table 1 Handling of Quantitative Laboratory Measurements

Chemistry			
Parameter	**Result**	**Findings in Laboratory ADaM Dataset**	**Mapping**
Bilirubin	<2	Upper limit of normal is <17 (ANRHI), no lower limit reported (ANRLO). Some baseline, most post-baseline results. Post-baseline results noted as normal.	Only value to be mapped: <2 µmol/L. Mapping: <2 µmol/L to 1 µmol/L. Rationale: Below ANRHI and no ANRLO for the parameter.
Creatinine	<18	Upper limit of normal is 36 (ANRHI), lower limit reported is 21 (ANRLO). Some baseline, most post-baseline results. Post-baseline results noted as abnormal.	Only value to be mapped: <18 µmol/L. Mapping: <18 µmol/L to 17 µmol/L. Rationale: Below ANRLO (21) for the parameter.

ADaM = Analysis Data Model. ANRHI = Analysis normal range upper limit. ANRLO = Analysis normal range lower limit.
Data review performed, and recommendations provided for handling of quantitative laboratory parameters by Study Sponsor. Binding antibodies and inhibitor parameter results are not to be mapped for calculation of e.g., geometric means, as this will result in biased estimates.

In addition, for the other lab values with "<" or ">", the following rules will be used:

Numeric Lab Values with	Actual Lab Values
>	Numerical part + 0.1
<	Numerical part - 0.1

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

- Hematology:
  - Hemoglobin, hematocrit, red blood cell count, and white blood cell count with differential (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.

[redacted]

For hematology, clinical chemistry [redacted] summary statistics on observed and change from baseline result and shift tables are to be presented by year of BAX 855 exposure 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 Pharmacokinetic Evaluations

The following information on PK evaluations is to be recorded in the eCRF:

- Pharmacokinetic (*Pharmacokinetic Sample Record* eCRF panel)
- IR sampling information (*FVIII Activity Sampling for Determination of Incremental Recovery* eCRF panel)
- IR infusion information (*FVIII Activity Infusion for Determination of Incremental Recovery* eCRF panel)

The actual results for PK and IR are to be obtained from Q^2 Solutions.

Pharmacokinetic parameters are to be derived using SAS® (SAS Institute Inc, 2017) or Phoenix® WinNonlin® Professional Version 6.4 (Certara L.P., Princeton, New Jersey).

The following derivations based on information recorded in the eCRF are to be performed:

- Prior to the estimation of PK parameters, FVIII activity levels reported as BLQ are to be treated numerically as zero. To ensure that FVIII present at Baseline (pre-infusion) is not attributed to the calculation of PK parameters, all post-infusion FVIII activity values ~~are to~~ be corrected for pre-infusion FVIII activity using the method described by ~~(~~Björkman et al~~, 2012)~~. This pre-infusion correction ~~is to~~ be performed as:

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

  where $C_{measured,tmax}$, is the observed maximum concentration at the associated visit.
- Incremental recovery is to be derived (by Q^2 Solutions) as:

$$IR[(\text{IU/dL})/[(\text{IU/kg})] = \frac{C_{max} - C_{pre-infusion}}{Dose[IU/kg]},$$

  where C_{max} is the observed concentration at the 15-30 minute sampling timepoint and $C_{pre-infusion}$ is the measured pre-dose concentration.
- Half-life ($t_{1/2}$) (hours) is to be calculated for subjects in the main study at baseline visit, visit 1 or visit 2 (if performed) and for FVIII inhibitor treatment subjects of the study (if performed). Since only an abbreviated PK assessment is to be performed to determine half-life with two post infusion blood draws at 15-30 minutes and 24-48 hours after infusion, the terminal phase to calculate half-life only includes two timepoints.
- The geometric coefficient of variation is to be derived as:

$$GeoCV = \sqrt{\exp(s^2) - 1} \times 100\%,$$

  where s refers to the SD of log transformed value.

All PK analyses are to use the actual sampling times, not nominal times. Actual sampling times are to be 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 to be a reason to exclude an observation. However, samples with unknown draw time and/or where the concentration could not be determined, or where results were deemed to be unreliable due to analytical issues, are to be eliminated before the calculations and are to be flagged as such in the by-subject-listings.

FVIII activities and IR over time are to be summarized using descriptive statistics by visit separately for subjects in the main study and FVIII inhibitor treatment subjects by treatment regimen for the PKAS. FVIII activities that are BLQ are to be treated as zero for computation of descriptive statistics (n, mean, SD, median, minimum, maximum, Q1, Q3 and IQR). PK parameters are to be summarized using n, mean, geometric mean, median, SD, geometric coefficient of variation, minimum, maximum, and 90% confidence intervals separately for subjects in the main study and FVIII inhibitor treatment subjects for the PKAS.

PK blood sample collection times as well as derived sampling time deviations are to be listed separately for subjects in the main study and FVIII inhibitor treatment subjects for the PKAS. A subject listing of individual PK parameters by visit is to be provided separately for subjects in the main study and FVIII inhibitor treatment subjects (with subsets for high-dose and low-dose regimens) for the PKAS.

8.4 Inhibitor/Antibody Development

The incidence of FVIII inhibitor development is the primary outcome measure for this study. The forming of binding antibodies is part of the secondary outcome measures for this study.

All subjects are to be tested for inhibitory antibodies to FVIII and binding IgG and IgM antibodies to FVIII, PEG-FVIII (BAX 855) and PEG. In case of a severe hypersensitivity reaction, an additional blood sample must be drawn to test for the presence of immunoglobulin E (IgE) antibodies against FVIII and PEG.

The following information on inhibitory/binding antibody development is to be recorded in the eCRF:

- Central laboratory information (*Central Lab Collection* eCRF panel)
- Confirmation in FVIII inhibitors (*Determination / Confirmation of FVIII Inhibitors* eCRF panel)
- Confirmation of inhibitor from local laboratory (*Confirmation of inhibitor - Local Lab* eCRF panel)
- Confirmation of inhibitor form central laboratory (*Confirmation of inhibitor - Central Lab* eCRF panel)

The actual laboratory results are to be obtained from the central laboratory.

Inhibitor and binding antibody results (including the titer, should the result be positive) specific to the forming of antibodies include:

- Inhibitory antibodies to FVIII
  - [redacted]
    - BAX 855
    - PEG
- Binding IgM antibodies to:
  - FVIII
  - BAX 855
  - PEG
- Binding IgE antibodies to:
  - FVIII
  - PEG

The following derivations based on information recorded in the eCRF are to be performed:

- A subject is considered as developed confirmed FVIII inhibitors if eCRF question "Has the central laboratory confirmed the FVIII inhibitor with a second repeat blood sample?" is answered "Yes" as obtained from *Determination / Confirmation of FVIII Inhibitors* eCRF panel.
- Assignment to a positive or negative result for inhibitory antibodies to FVIII, according to the Nijmegen modification of the Bethesda assay, is to be as follows:
  - Positive for inhibitor development with titer of ≥ 0.6 BU
  - Negative for inhibitor development with titer of < 0.6 BU
- Assignment to a positive, negative or not applicable result for IgG and IgM antibodies to FVIII, BAX 855 and PEG is to be done as follows:
  - Not applicable: Any result recorded as "NA"
  - Positive: Any result recorded with a dilution larger than 1/80 or where the change from baseline indicates an increase in titer steps of two or more

steps (i.e., 1/80 to 1/320, or 1/160 to 1/640 or 1/320 to 1/1280 or 1/640 to 1/2560)

- Negative: Any result not meeting the definition of "Not applicable" or "Positive"

- A FVIII inhibitor treatment success is defined as:
  - 1) A persistently negative inhibitor titer < 0.6 BU
  - 2) FVIII IR ≥ 66% of initial baseline value following a wash-out period of 84-96 h

    If no baseline IR is available, an IR value indicative of an adequate clinical response following a wash-out period of 84-96 hours is to be used for the definition of success. An adequate clinical response is defined as pharmacokinetic parameters that permit effective prophylactic treatment of the study subject, including maintenance of FVIII levels above 1%.

  - 3) A FVIII half-life of ≥ 6 hours.

  Note: this criteria is not applicable to EU countries (Please refer to EU protocol amendments: PA2, PA5, PA7, and PA8 EEA/UK).

- A FVIII inhibitor treatment partial success is defined after 33 months of FVIII inhibitor treatment, if two of the three criteria for a success are met.
- A FVIII inhibitor treatment failure is defined as the failure to meet the criteria for success or partial success within 33 months of FVIII inhibitor treatment OR less than 20% reduction in inhibitor titer, relative to the peak inhibitor titer, over any six-month period after the first three months of treatment.

The proportion of subjects who developed an inhibitor (development of neutralizing 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 subsets of subjects included in this analysis are:

- Subjects that developed inhibitory antibodies to FVIII (confirmed by the 2nd repeated blood sample within 2 weeks of the 1st positive blood sample) 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 for final analyses or 50 or more EDs for interim analyses.

The 50, or 100 EDs needed to be reached at the time of the last inhibitor test unless the subject was positive at any time.

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

```
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 a particular result and <result> to the actual result, i.e., "Yes" or "No".

Inhibitory antibodies to FVIII and binding antibodies to FVIII, BAX 855 and PEG are to be summarized for the SAS and IAS where applicable and listed for the ENR. Shift tables are presented by year of BAX 855 exposure. [redacted]

[redacted]

Kaplan Meier (K-M) curves will be generated to display FVIII inhibitor occurrence vs EDs for all subjects in the SAS who develop inhibitors and subjects who stay in the study for less than 50 EDs or 50/100 or more EDs and develop no inhibitors. The proportion of subjects that developed FVIII inhibitors is to be displayed on the y-axis and the EDs is to be displayed on the x-axis. All subjects included in the SAS are to be used in this figure. Censored subjects are to refer to subjects that did not developed FVIII inhibitors i.e., completed the study without developing FVIII inhibitors. The presentation is to be based on inhibitor confirmation date.

In addition, Kaplan Meier curves will be generated with the high and low titer inhibitors representing 2 separate curves.

Subjects with high or low inhibitor titers will be listed.

Time to FVIII inhibitor treatment success including time to 1st negative test and 2nd negative test will be summarized descriptively. Time to FVIII inhibitor treatment success

will be calculated as the date of the 1st/2nd negative tests – the date of the first FVIII inhibitor treatment (ITI) +1;

In addition, the risk factors for the development of inhibitors, including exposure of dosage (IU, IU/kg) prior to the inhibitor onset, number of EDs prior to the inhibitor onset, surgeries (yes/no) prior to the inhibitor onset, and mutation (FVIII gene) will also be explored.

8.5 Vital Signs

Vital signs are to be measured at screening and pre-infusion (within 15 minutes before administration of IP) and post-infusion (15 to 30 minutes after administration of IP).

Information on vital signs is to be recorded in the eCRF (*Vital Signs* eCRF panels).

The following derivations based on information recorded in the eCRF are to be performed:

- A result is 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").
- Age for age group in Table 2 is to be calculated using the following formula:
  - If age at informed consent is in years, convert to months using the following formula:

$$Age\ in\ months = Age\ in\ years * 12.$$

  - Calculate age for age group in months using the following formula:

$$Age[months] = (Vital\ Signs\ collection\ date - Date\ of\ informed\ consent)[months] + Age\ at\ informed\ consent[months].$$

  - If Age [months] is greater than 12 convert to years using the formula specified in Section 6.2: Demographic and Baseline Characteristics.
  - Round calculated age down.
- Normal ranges for vital signs are to be based on the age specific normal ranges as defined by (Agrawal, 2008) and set out in Table 2 below.

Table 2 Age Specific Normal Ranges for Vital Signs

Parameter	Age Group	Normal Range
Pulse Rate (bpm)	0-<3 months	100 – 150
	3-<6 months	90 – 120

Parameter	Age Group	Normal Range
	6-<12 months	80 – 120
	1-<3 years	70 – 110
	3-<6 years	65 – 110
	6-10 years	60 – 95
Respiratory Rate (breaths/min)	0-<3 months	35 – 55
	3-<6 months	30 – 45
	6-<12 months	25 – 40
	1-<3 years	20 – 30
	3-<6 years	20 – 25
	6-10 years	14 – 22
Temperature* (°C)	0-2 years	34.72 – 37.28
	3-10 years	35.89 – 36.67
Systolic Blood Pressure (mmHg)	0-<3 months	55 – 75
	3-<6 months	65 – 85
	6-<12months	80 – 100
	1-<3 months	90 – 105
	3-<6 years	95 – 110
	6-10 years	100 – 120
Diastolic Blood Pressure (mmHg)	0-<3 months	45 – 55
	3-<6 months	50 – 65
	6-<12 months	55 – 65
	1-<3 years	55 – 70
	3-10 years	60 – 75

*Normal ranges for armpit used.

Summary statistics on observed and change from baseline results as well as a shift table by year of BAX 855 exposure are to be presented for vital signs for the SAS. Vital signs results are to be listed for the SAS.

8.6 Physical Examination

Information on physical examination is to be recorded in the eCRF (*Physical Examination* eCRF panel).

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

8.7 Comments

Information on comments is to be recorded in the eCRF (*Comments* eCRF panels).

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

9. ANALYSIS SOFTWARE

All analyses are to be conducted using SAS® (SAS Institute Inc, 2017) software package, Version 9.4 or later. PK analyses are to be conducted using the software noted in Section 8.3: Pharmacokinetic Evaluations.

10. REFERENCES

Agrawal, S. (2008). Normal Vital Signs in Children: Heart Rate, Respirations, Temperature, and Blood Pressure. Complex Child E-Magazine. Viewed 28 March 2019. Retrieved from *http://www.articles.complexchild.com/march2009/00114.pdf*

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

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11. REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	2019 JUN 07	New Document
1.1	2019 NOV 20	• Co-author added, because initial author is no long part of IQVIA Team. • Updated prophylaxis analysis set (PAS) definition. • Updated hemostatic efficacy analysis set (HEAS) definition, • Removed reference to section 5.2 in section 5.1. • Updated section 5.4 to include linear interpolation in the event that body weight is not available. • Added information to section 6.1 for subjects who received prophylaxis only, on-demand only, both prophylaxis and on-demand, and at least one infusion for inhibitor treatment. • Added relevant units in section 6.2 for baseline demographics and disease characteristics. • Added text to section 7.1 for the use of the univariate procedure and for the glimmix procedure in the event of non-convergence. • Improved text for blood loss and hemostatic efficacy (global and overall primary) in section 7.2. • Improved section 8.3 by clarifying the calculation for baseline-adjusted FVIII activity level, specifying the team performing the derivation of incremental recovery,

		removing the text "pre-dose" to reporting of FIII activity levels, and removing the $t_{1/2}$ text.
2.0	2020 MAR 06	• Improved text regarding the confidence interval as documented in section 7.1. • Improved section 8.2 for handling quantitative laboratory values using current identified laboratory results.
3.0	2023 SEP 21	• Added analysis of ABR for less than 6 months and 12 months or longer in Section 7.1 • Added analysis of ABR for different dose frequencies in Section 7.1 • A new analysis set, Long Term Safety Analysis Set (LTSAS) has been added. • Added the safety analysis for subjects who had the study treatment for 5 years or more (LTSAS) in Section 8.1 • Added KM curves by inhibitor titer in Section 8.4 • Added the analysis of the risk factors of the development of inhibitor by exposures in Section 8.4