CLINICAL STUDY PROTOCOL

PRODUCT: BAX 855

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

STUDY SHORT TITLE: BAX 855 Continuation

PROTOCOL IDENTIFIER: 261302

CLINICAL TRIAL PHASE 3b

AMENDMENT 7: 2015 MAR 20 (GLOBAL)

Replaces: AMENDMENT 4: 2014 MAY 23 (GLOBAL)

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NCT Number: NCT01945593
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Study Sponsor(s):

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1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

Barbara Valenta-Singer, MD
PPD Clinical Development
Baxalta US Inc.

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (eg, investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ECs.

ALL SAEs ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT

See SAER form for contact information.
Further details are also available in the study team roster.

For definitions and information on the assessment of these events, refer to the following:

- AE, Section 12.1
- SAE, Section 12.1.1.1
- Assessment of AEs, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	BAX 855
Name(s) of Active Ingredient(s)	PEGylated recombinant factor VIII (PEG-rFVIII)
CLINICAL CONDITION(S)/INDICATION(S)	
• Previously treated patients (PTPs) with severe hemophilia A (FVIII <1%)	
PROTOCOL ID	261302
PROTOCOL TITLE	A Phase 3b Continuation study of the Safety and Efficacy of PEGylated Recombinant Factor VIII (PEG-rFVIII; BAX 855) in Prophylaxis of Bleeding in Previously Treated Patients with Severe Hemophilia A
Short Title	BAX 855 Continuation
STUDY PHASE	Phase 3b
PLANNED STUDY PERIOD	
Initiation	2013 OCT
Primary Completion	2017 Q4
Study Completion	2017 Q4
Duration	The overall duration of the study is estimated to be approximately 4 years from study initiation to last subject last visit.
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
• To continue the evaluation of the safety and efficacy of BAX 855 for prophylaxis and treatment of bleeding episodes in adult and pediatric PTPs aged ≤ 75 years of age with severe hemophilia A.	
Primary Objective	
The co-primary objectives of the study are: 1. To determine the safety of BAX 855 based on the incidence of FVIII inhibitory antibody development 2. To determine the efficacy of BAX 855 based on the annualized bleed rate (ABR) of spontaneous bleeding episodes	
Secondary Objective(s)	
Efficacy 1. To determine the total ABR (spontaneous and traumatic bleeding episodes) 2. To determine the overall hemostatic efficacy rating of BAX 855 for treatment of breakthrough bleeding episodes 3. To determine the length of intervals between bleeding episodes 4. To characterize the hemostatic efficacy of BAX 855 for treatment of bleeding episodes by the number of BAX 855 infusions for treatment 5. To determine total weight-adjusted consumption of BAX 855 for prophylaxis and for treatment of bleeding episodes 6. To assess Patient Reported Outcomes (PROs) over time for subjects receiving BAX 855	

Safety

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

Exploratory Objective

- To assess patient satisfaction, patient activity levels, and health resource use over time for subjects receiving BAX 855
- To determine the potential correlation between thrombin generation assay (TGA) parameters, FVIII trough levels and ABR

STUDY DESIGN

Study Type/ Classification/ Discipline	Safety and Efficacy
Control Type	No Control
Study Indication Type	Prevention and Treatment
Intervention model	Parallel
Blinding/Masking	Open-label
Study Design	This is a phase 3b, prospective, open label, multi-center study to evaluate the safety and efficacy of BAX 855 for prophylactic use and the control of bleeding episodes in approximately 200 pediatric and adult PTPs ≤ 75 years of age with severe hemophilia A. The study plans to include subjects from other BAX 855 studies and BAX 855-naïve subjects. Subjects will receive either a fixed dose prophylaxis with BAX 855 consisting of 45 ± 5 IU/kg for subjects aged ≥ 12 years or 50 ± 10 IU/kg for subjects aged < 12 years twice weekly or, subjects can decide to receive a pharmacokinetically-tailored (PK-tailored) prophylactic BAX 855 dosing regimen based on the subject's individual PK to maintain FVIII trough levels of ≥3%. The frequency of PK-tailored prophylactic BAX 855 dosing will be at least twice weekly.
Planned Duration of Subject Participation	Each subject will participate in the study until a total of at least 100 exposure days (EDs) to BAX 855 has been achieved (accumulated across all BAX 855 studies in which each subject participated). Depending on the subject's BAX 855 exposure history and treatment regimen given, the planned duration of subject participation to reach the 100 EDs can vary from approximately 3 to 12 months. However, extension of the study duration for individual subjects beyond the 100 EDs may be granted.

Primary Outcome Measure

Safety: Development of inhibitory antibodies to FVIII
Efficacy: Spontaneous ABR

Secondary Outcome Measure(s)

Efficacy

1. Total ABR (spontaneous and traumatic bleeding episodes)
2. Overall hemostatic efficacy rating of BAX 855 for treatment of breakthrough bleeding episodes
3. Number of BAX 855 infusions to treat bleeding episodes

4. Time intervals between bleeding episodes 5. Weight-adjusted consumption of BAX 855 **Safety** 1. Occurrence of AEs and serious adverse events (SAEs) 2. Changes in vital signs and clinical laboratory parameters (hematology, clinical chemistry, and lipids) 3. Immunogenicity a. Binding antibodies (IgG and IgM) to FVIII, BAX 855, and PEG b. Anti-Chinese hamster ovary (CHO) antibodies **Patient Reported Outcomes (PROs)** Changes from baseline in parent study, if applicable, in the following: 1. Bleed and pain severity as measured using the Haemo-SYM questionnaire 2. Health-related quality of life (HRQoL) as assessed using the SF-36/PedsQL questionnaires
Exploratory Outcome Measure(s)
1. Patient satisfaction with treatment will be assessed using the Satisfaction Question Set 2. Patient Activity Level 3. Health resource use data (eg, physician office visits, hospitalizations, days missed from work/school) 4. TGA parameters, FVIII trough levels and ABR
INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION

Active Product	**BAX 855** **Dosage form**: injection, powder, lyophilized, for solution. **Dosage frequency**: • Fixed prophylactic regimen: o Subjects aged ≥ 12 years: 45 ± 5 IU/kg twice weekly, which may be increased up to 80 IU/kg o Subjects aged < 12 years: 50 ± 10 IU/kg twice weekly, which may be increased up to 80 IU/kg OR • PK-tailored prophylactic BAX 855 regimen based on subject's individual PK profile to maintain a FVIII trough level of ≥3%. However, the dosing regimen should not exceed 80 IU/kg for any single infusion and the FVIII peak levels should not exceed 200%. **Mode of Administration**: intravenous bolus infusion
SUBJECT SELECTION	
Targeted Accrual	Approximately 250 PTPs with severe hemophilia A.
Number of Groups/Arms/Cohorts	Two: Fixed BAX 855 prophylaxis or PK-tailored BAX 855 prophylaxis

Inclusion Criteria

Subjects transitioning from other BAX 855 studies

Subjects transitioning from other BAX 855 studies who meet **ALL** of the following criteria are eligible for this study:

1. Subject has completed a previous BAX 855 study and is willing to immediately transition into this continuation study.[i]
2. Subject is ≤ 75 years of age at screening of the previous BAX 855 study.
3. Subject continues to have a Karnofsky (for subjects aged ≥ 16 years) or Lansky (for subjects aged < 16 years) performance score of ≥ 60 (see Section 20.5).
4. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm^3, as confirmed by central laboratory at screening.
5. Subject is hepatitis C virus negative (HCV-) by antibody or PCR testing (if positive, antibody titer will be confirmed by PCR), as confirmed by central laboratory at screening; or HCV+ with chronic stable hepatitis.
6. If female of childbearing potential, subject presents with a negative urine pregnancy test and agrees to employ adequate birth control measures for the duration of the study.
7. Subject and/or legally authorized representative is willing and able to comply with the requirements of the protocol.

BAX 855 naïve subjects

BAX 855 naïve subjects who are ≥ 12 years of age can only be enrolled in this continuation study after enrollment in the phase 2/3 pivotal study is closed. BAX 855 naïve subjects who are < 12 years of age can only be enrolled in this continuation study after enrollment in the pediatric PTP study is closed.

Enrolment of BAX 855 naïve subjects will only start once the sponsor has notified the study sites accordingly.

BAX 855 naïve subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject is ≤75 years of age at screening.
2. Subject is naïve to BAX 855.
3. Subject has severe hemophilia A (FVIII clotting activity < 1%) as confirmed by central laboratory at screening after at least a 72-hour washout period.[ii]
4. Subject aged ≥ 6 years has documented previous treatment with plasma-derived FVIII concentrates or rFVIII for ≥ 150 EDs.
5. Subject aged < 6 years has documented previous treatment with plasma-derived FVIII concentrates or rFVIII for ≥ 50 EDs.
6. Subject is currently receiving prophylaxis or on-demand therapy with FVIII.

[i] NOTE: Subjects who have received FVIII concentrates other than BAX 855 following completion of the previous BAX 855 study are excluded from participation in this continuation study.

ii If FVIII activity is ≥1%, severe hemophilia A classification can be confirmed by historically documented FVIII clotting activity < 1% performed by a certified clinical laboratory or by a documented genotype known to result in severe hemophilia A.

7. Subject has a Karnofsky (for subjects aged ≥ 16 years) or Lansky (for subjects aged < 16 years) performance score of ≥ 60 (see Section 20.5).
8. Subject is HIV-; or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm^3, as confirmed by central laboratory at screening.
9. Subject is HCV- by antibody or PCR testing (if positive, antibody titer will be confirmed by PCR), as confirmed by central laboratory at screening; or HCV+ with chronic stable hepatitis.
10. If female of childbearing potential, subject presents with a negative urine pregnancy test and agrees to employ adequate birth control measures for the duration of the study.
11. Subject and/or legally authorized representative is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects transitioning from other BAX 855 studies

Subjects transitioning from other BAX 855 studies who meet **ANY** of the following criteria are not eligible for this study:

1. Subject had detectable FVIII inhibitory antibodies (≥ 0.6 BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening.
2. Subject has developed FVIII inhibitory antibodies (≥ 0.6 BU using the Nijmegen modification of the Bethesda assay as determined at central laboratory in a previous BAX 855 study).
3. Subject has acquired a hemostatic defect other than hemophilia A (eg, qualitative platelet defect or von Willebrand's disease) in a previous BAX 855 study.
4. Subject has severe chronic hepatic dysfunction (eg, ≥ 5 times upper limit of normal alanine aminotransferase [ALT], as confirmed by central laboratory at screening).
5. Subject has severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening.
6. Subject experienced a life-threatening or gastrointestinal bleeding episode within 3 months prior to study entry.
7. Subject is scheduled to use other PEGylated drugs during study participation.
8. Subject is planning to take part in any other clinical study during the course of the continuation study, with the exception of any other parallel BAX 855 study.
9. Subject has medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance.
10. Subject is a family member or employee of the investigator.

BAX 855 naïve subjects

BAX 855 naïve subjects who meet **ANY** of the following criteria are not eligible for this study:

1. Subject has detectable FVIII inhibitory antibodies (≥ 0.6 BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening.
2. Subject has 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.
3. Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (eg, qualitative platelet defect or von Willebrand's disease).
4. Subject has known hypersensitivity towards mouse or hamster proteins, PEG, or Tween 80.

5. Subject has severe chronic hepatic dysfunction (eg, ≥ 5 times upper limit of normal ALT, as confirmed by central laboratory at screening).
6. Subject has severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening.
7. Subject experienced a life-threatening or gastrointestinal bleeding episode within 3 months prior to study entry.
8. Subject has current or recent (< 30 days) use of other PEGylated drugs prior to study participation or scheduled use of such drugs during study participation.
9. Subject has participated in another clinical study involving an IP other than BAX 855 or 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.
10. Subject has medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance.
11. Subject is a family member or employee of the investigator.

STATISTICAL ANALYSIS

Sample Size Calculation

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

Planned Statistical Analysis

Analysis of Primary Outcome Measures

Safety:

The number and proportion (Clopper-Pearson exact 95% CI) of subjects having been exposed to BAX 855 who develop inhibitory antibodies to FVIII (≥0.6 BU) will be provided.

Efficacy:

The spontaneous ABR will be assumed to have a negative binomial distribution, and the mean ABR (95% CI) will be estimated using a general estimating equation (GEE) model framework (with a logarithmic link function which is the default for the negative binomial distribution) with treatment regimen as a fixed effect, subject effect as a random effect, age at baseline as a continuous covariate, and the logarithm of follow-up time (in years) as an offset.

Analysis of Secondary Outcome Measures

Efficacy:

The total ABR (spontaneous and traumatic bleedings) will be estimated and described similarly as the primary efficacy outcome measure.

The efficacy of BAX 855 in the treatment of bleeds will be summarized. It includes overall hemostatic efficacy rating at 24 (±2) hours after initiation of treatment and at resolution of bleed, number of BAX 855 infusions to control bleeding and total weight-adjusted dose per bleeding episode (excluding any infusions given to maintain hemostasis after the bleeding was controlled), and time interval between bleeding episodes.

Frequency tables will be prepared for the number of BAX 855 infusions required for the treatment of bleeding episodes. The median number of infusions (and nonparametric 95% CI) will be estimated.

Weight-adjusted consumption of BAX 855 for prophylaxis, treating bleeding episodes (excluding any infusions given to maintain hemostasis after the bleeding is controlled) and in total per subject will be summarized separately as average number of BAX 855 infusions and average weight-adjusted consumption of BAX 855 per month.

The average time interval between 2 consecutive bleeding episodes will be computed for each subject as the duration of the observation period divided by the number of bleeding episodes in the observation period. The median (95% CI) of those average time intervals between 2 bleeding episodes will be estimated.

Pharmacokinetics:

For subjects undergoing a pharmacokinetic (PK) assessment in this study, the following PK parameters for FVIII will be reported using descriptive statistics: area under the plasma concentration curve from 0 to infinity ($AUC_{0-\infty}$), half-life ($T_{1/2}$), mean residence time (MRT), total body clearance (CL), incremental recovery over time (IR), maximal plasma concentration (Cmax), and volume of distribution at steady state (Vss).

For subjects undergoing a PK assessment in this study, an exploratory analysis of correlation of baseline von Willebrand factor (VWF) antigen to BAX 855 PK will be performed as well as the possible influence of any anti-PEG antibodies (preexisting or detected during study participation) on the PK of BAX 855, if applicable.

IR will be summarized by visit and displayed graphically over time for each subject. Also the change from the baseline will be described using summary statistics.

Safety:

Frequency counts and percentages will be calculated for SAEs, occurrence of inhibitory antibodies to FVIII, occurrence of binding antibodies to FVIII, BAX 855, PEG, occurrence of anti-CHO antibodies, occurrence of severe allergic reactions, and occurrence of thrombotic events.

AEs that occurred during or after treatment will be presented in summary tables. AEs will be cross-tabulated for relatedness, seriousness, and severity. AEs will be categorized according to the MedDRA dictionary and summarized by system organ class and preferred term.

Vital signs and laboratory parameters will be characterized descriptively. Shift tables will be prepared for laboratory parameters. Clinically significant abnormal values in routine laboratory parameters (hematology, clinical chemistry, lipids) and vital signs will be summarized.

Patient Reported Outcomes (PROs):

Bleed and pain severity will be measured using the Haemo-SYM questionnaire with higher scores on the Haemo-SYM indicating more severe symptoms. Changes from baseline in the Haemo-SYM scores will be tested for statistical significance using a Wilcoxon test for paired samples. Number and proportion of subjects with an improvement in the Haemo-SYM pain subscale will be tabulated.

HRQoL will be measured using the SF-36 questionnaire with lower scores on SF-36 indicating worse HRQoL. Changes from baseline in the SF-36 scores will be tested for statistical significance using a Wilcoxon test for paired samples. The number and proportion of subjects with an improvement in SF-36 will be tabulated.

HRQoL in subjects aged < 14 years will be measured using the PedsQL with lower scores on the PedsQL indicating worse HRQoL. Changes from baseline to end of study in the PedsQL scores will be tested for statistical significance using a Wilcoxon test for paired samples. Number and proportion of subjects with an improvement in the PedsQL will be tabulated.

Analysis of Exploratory Outcome Measures

Patient satisfaction with treatment, patient activity level and health resource use data will be descriptively summarized and listed.

TGA parameters (lag time, time to peak thrombin generation, peak thrombin generation, and endogenous thrombin potential [ETP]) will be presented descriptively and displayed graphically. The potential influence of TGA parameters and FVIII trough levels on ABR in the three months after TGA/FVIII trough level measurement will be explored by scatterplots where TGA is performed.

Interim Safety Reviews

A first interim safety review will be performed for marketing authorization application to the European Medicines Agency (EMA).

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

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	annualized bleed rate
AE	adverse event
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
AUC(0-∞)	area under the plasma concentration curve from 0 to infinity
BAX 855	product code name for Baxalta's PEGylated recombinant FVIII (rFVIII)
BU	Bethesda unit
US CFR	US Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
CL	total body clearance
Cmax	maximum plasma concentration
(e)CRF	(electronic) case report form
DMC	data monitoring committee
EC	ethics committee
ED	exposure day
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ETP	Endogenous thrombin potential
FDA	US Food and Drug Administration
FVIII	factor VIII
GCP	Good Clinical Practice
GEE	general estimating equation
HAV	hepatitis A virus
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HDL	high density lipoprotein
HIV	human immunodeficiency virus

Abbreviation	Definition
HRQoL	health-related quality of life
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ICF	informed consent form
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IP	investigational product
ITI	immune tolerance induction
IU	international unit (s)
IR	incremental recovery over time
IQR	Interquartile ranges
i.v.	intravenous(ly)
LDL	low density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
Mo	Month
MRT	mean residence time
NMC	non-medical complaint
PCR	polymerase chain reaction
pdFVIII	plasma-derived factor VIII
PedsQL	Pediatric Quality of Life Inventory
PEG	polyethylene glycol
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PP	per protocol
PRO	patient reported outcomes
PTP	previously treated patient
PUP	previously untreated patient
q5d	Dose every five (5) days
q7d	Dose every seven (7) days
rFVIII	recombinant factor VIII
SAE	serious adverse event

Abbreviation	Definition
SAER	serious adverse event report
SF-36	Short form-36 questionnaire
SIC	subject identification code
SWFI	sterile water for injection
$T_{1/2}$	half life
TGA	Thrombin generation assay
Tmax	time to maximum concentration in plasma
US	United States
VLDL	very low density lipoprotein
Vss	volume of distribution at steady state
VWF	von Willebrand Factor

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

The investigational product (IP), BAX 855, is a novel polyethylene glycol (PEG)-ylated full-length recombinant factor VIII (rFVIII) molecule. BAX 855 is intended for use as a FVIII replacement therapy with an extended half-life in the prophylaxis and treatment of bleeding events in patients with severe hemophilia A.

Current management of severe hemophilia A includes on-demand treatment for bleeding events and prophylaxis to prevent bleeds.[1; 2] The average half-life of current FVIII products is in the range of 12-14 hours,[3; 4] thus current prophylaxis regimens require infusion of FVIII every other day, or every 2 to 3 days when based on the subject's individual pharmacokinetic (PK) profile.[5] BAX 855 is characterized by controlled PEGylation of full length recombinant FVIII and designed to extend the half-life of FVIII. BAX 855 may improve the treatment of hemophilia A by providing the opportunity to reduce the frequency of administration during prophylaxis while maintaining similar therapeutic benefits to existing FVIII products, improve subject convenience and compliance with therapy, and thereby improving overall health outcomes.

The rFVIII of BAX 855 is identical to the full-length albumin/plasma free manufactured octocog alfa known as ADVATE. The product is expressed in Chinese hamster ovary (CHO). PEG chains (20 kDa) are covalently bound to the rFVIII protein using a stable linker. The BAX 855 product is reconstituted with sterile water for injection (SWFI) and administered intravenously (i.v.) as a solution by bolus infusion. It uses the same stabilizing agents (mannitol, trehalose, histidine, and glutathione) as the parent rFVIII product (octocog alfa, ADVATE). Comprehensive preclinical studies as well as a successfully completed phase 1 study (Baxter clinical study 261101) have shown that the PEGylation extends both the *in vivo* half-life and the measurable circulating activity of the product (as determined by chromogenic and 1-stage clotting assays). Physiochemical characterization studies demonstrate that the functional activity of BAX 855 is comparable to that of ADVATE. Additional details can be found in the BAX 855 Investigator Brochure (IB).

The clinical development program for BAX 855 follows the European Medicines Agency (EMA) guidance outlined in EMA/CHMP/BPWP/144533/2009[6] and consists of 1 completed, 4 ongoing and 2 planned studies (see Table 1).

Table 1
BAX 855 Clinical Development Program

Study Number	Type of Study Criteria for inclusion	Study Status
261101	Phase 1 PTP; 18-65 years	Completed
261201	Pivotal Phase 2/3 PTP; 12-65 years	Ongoing
261202	Pediatric PTP Phase 3 PTP; <12 years	Ongoing
261204	Surgery Phase 3 PTP; participated in other BAX 855 studies or BAX 855 naïve; 2-75 years	Ongoing
261302	Continuation Phase 3b PTP; participated in other BAX 855 studies or BAX 855 naïve; ≤75 years	Ongoing
261203	Pediatric PUP Phase 3 PUP; <6 years	Planned
261303	PK-guided Phase 3 PTP; 12-65 years	Planned

A Phase 1 study in previously treated patients (PTPs) aged 18 to 65 years with severe hemophilia A (Baxter Clinical Study **261101**) to evaluate the safety and PK of BAX 855 at doses of 30 IU/kg and 60 IU/kg has been completed. The results showed that a single infusion of BAX 855 was safe and well tolerated. The terminal half-life was extended 1.4 to 1.5 fold as compared to ADVATE.

A Phase 2/3 pivotal study is ongoing since January 2013 (Study **261201**) and investigates PK properties in 25 subjects of whom at least 6 subjects are adolescents, as well as hemostatic efficacy, safety and immunogenicity in approximately 132 PTPs aged ≥ 12 years with severe hemophilia A (115 receiving prophylactic treatment and 17 receiving on-demand treatment) in the control and prophylaxis of bleeding episodes.

A pediatric study (Study **261202**) will evaluate the PK, efficacy, safety, and immunogenicity of BAX 855; 60 pediatric subjects (30 subjects aged <6 years and 30 subjects aged ≥6 to <12 years) with severe hemophilia A will be enrolled to have 50 evaluable subjects (25 in each age cohort) receiving twice weekly prophylactic treatment with 50 ±10 IU/kg of BAX 855 over a period of 6 months or at least

50 exposure days (EDs), whichever will occur last. A subset of 28 subjects (14 in each age cohort) will participate in the PK portion of the study which will be performed prior to the start of prophylactic treatment.

A Phase 3 study to evaluate the efficacy and safety of BAX 855 in the perioperative management in subjects undergoing major or minor elective, or minor emergency surgical/invasive procedures is currently ongoing (Study **261204**). Approximately 40 PTPs with severe hemophilia A (FVIII <1%) will be enrolled who are expected to require approximately 50 major or minor elective or minor emergency surgeries or other invasive procedures. At least 10 procedures in at least 5 PTPs have to be major. The dose and frequency of BAX 855 administered will be guided by each subject's PK profile using a single dose infusion of 60 ±5 IU/kg BAX 855 for major surgeries and BAX 855 incremental recovery (IR) for minor surgeries.

A Phase 3 study to evaluate the efficacy and safety of BAX 855 in previously untreated patients (PUPs) < 6 years of age with severe hemophilia A (Study **261203**) will be initiated once data are available from the pediatric study **261202** from 20 patients with 50 EDs each, including a minimum of 10 patients <6 years, and when PK investigations in children <12 years are completed. In total, 110 subjects will be enrolled to have 100 evaluable PUPs. There will be 2 prophylactic treatment arms of either 30 IU/kg or 45 IU/kg BAX 855 administered twice weekly for ≥50 EDs.

A Phase 3 study will assess the safety and efficacy of PK-guided treatment with BAX 855 targeting two different FVIII trough levels (Study **261303**). A total of 120 subjects, 12 to 65 years old, with severe hemophilia A will be recruited, to have 104 evaluable subjects (52 per treatment arm).

In this continuation study (Study 261302), subjects will receive either a fixed dose prophylaxis with BAX 855 consisting of 45 ± 5 IU/kg for subjects aged ≥ 12 years or 50 ± 10 IU/kg for subjects aged < 12 years twice weekly or, subjects can decide to receive a PK-tailored prophylactic BAX 855 dosing regimen based on the subject's individual PK to maintain FVIII trough levels of ≥3%.

The fixed-dose prophylactic treatment regimens in this continuation study (45 ± 5 IU/kg twice weekly for subjects aged ≥ 12 years, to be increased to 80 IU/kg if needed, and 50 ± 10 IU/kg twice weekly for subjects aged < 12 years, to be increased to 80 IU/kg if needed) are aligned with the dosing regimens used in the pivotal phase 3 study in subjects aged ≥ 12 years (Study 261201) and the pediatric PTP study in subjects aged < 12 years (Study 261202); with these dosing regimens the majority of subjects are assumed to maintain FVIII trough levels above 1% at all times. The increase to 80 IU/kg for subjects

aged ≥ 12 years as compared to the increase to 60 IU/kg in the pivotal study (Study **261201**) will provide more flexibility in the management of the subject.

Dose recommendations used in prophylaxis are usually designed to keep the FVIII trough level above 1% of the normal level[7] because of the strong correlation between increasing time spent at FVIII level less than 1% and increase of the ABR.[8] However, the 1% trough level is not applicable to prevent bleeding episodes in all patients. Especially patients with target joints or progressive hemophilic arthropathy often bleed in spite of maintenance of a 1 % trough level, although this association is difficult to assess in clinical practice.[9]

A pioneering bench mark study by Den Uijl et al. has suggested that the annual number of joint bleeds is asymptotically approaching zero when baseline levels of FVIII ≥ 10% are maintained.[10] According to this model, the maximum reduction of annual joint bleeds will be achieved if FVIII trough levels are raised from 1 to 3%. This assumption is confirmed by another study in patients with moderate hemophilia (FVIII 1–5%) which demonstrated a median number of joint bleeds of 0 (IQR: 0–1.2) in patients with > 3% residual plasma FVIII activity.[11]

For above outlined reasons, a FVIII target trough level of ≥ 3 % has been selected for the PK-tailored prophylactic treatment regimen in this continuation study. The approach of a PK-tailored prophylactic dosing regimen takes the generally observed marked inter-patient variability of PK parameters into account since the dose and frequency will be based on the patient's individual PK. It is expected that by ensuring FVIII trough levels of ≥3% the frequency of bleeding episodes may be substantially reduced.

The FVIII dosing for the treatment of bleeding episodes is aligned with recommendations in the EMA/CHMP/BPWP/1619/1999 rev.1.[12] Also, recommended doses as high as 60 ± 5 IU/kg for the treatment of bleeding episodes are based upon experience with these doses with ADVATE.

Overall exposure is based on the guideline EMA/CHMP/BPWP/144533/2009 for market authorization of FVIII products in which a minimum of 100 exposure days (EDs) in at least 200 subjects is recommended.[6]

6.2 Clinical Condition/Indication

Hemophilia A is an X-chromosome linked recessive, congenital bleeding disorder caused by deficient or defective coagulation due to deficiency of FVIII. The absence of FVIII leads to 'spontaneous' bleeding episodes (occurring primarily in joints, muscles, and less

commonly, in soft tissues) and to excessive bleeding following trauma or injury. Hemophilia A is currently treated with FVIII replacement using either plasma-derived (pdFVIII) or rFVIII concentrates.[13; 14]

The intended indication for BAX 855 is the treatment and prevention of bleeding in subjects with hemophilia A.

6.3 Population To Be Studied

Approximately 250 PTPs with severe hemophilia A, of any ethnic group, aged ≤75 years, will be enrolled to achieve a total of 200 evaluable subjects. Each subject will have ≥100 EDs with BAX 855, as accumulated across all BAX 855 studies in which the subject participates.

Justification for enrollment of pediatric subjects is based on the nonclinical safety requirements outlined in the ICH M3 Guideline, Section 12 as well as the ICH E11 Guideline on clinical investigation of medicinal products in the pediatric population. Hemophilia is a serious and potentially life-threatening disease. Pediatric subjects are expected to benefit from a full-length rFVIII molecule with an extended half-life. Moreover, results from nonclinical repeated toxicology studies, the core safety pharmacology package, and the clinical phase 1 study have not raised any safety or tolerability concerns. Furthermore, the parent protein molecule ADVATE has been used extensively in the entire pediatric population with no unforeseen adverse events (AEs) (refer to the ADVATE IB). BAX 855 naïve subjects <12 years of age will not be enrolled in this continuation study until enrollment in the BAX 855 pediatric PTP study in children aged <12 years (Study 261202) has been completed. In accordance with the EMA/CHMP/BPWP/144533/2009 guideline[6], the study in pediatric PTPs < 12 years of age (Study 261202) will only be initiated once PK, hemostatic efficacy and safety data of 20 PTPs aged ≥ 12 years treated with BAX855 for at least 50 EDs are available and evaluated by an independent DMC for its safety and efficacy. At least 60 evaluable subjects in this BAX 855 continuation study must be <12 years of age.

6.4 Findings from Nonclinical and Clinical Studies

6.4.1 Findings from Nonclinical Studies

BAX 855 is manufactured by covalently binding a branched PEG reagent with a molecular weight of 20 kDA to Baxalta's rFVIII (octocog alfa, ADVATE).

Baxalta's octocog alfa is expressed in CHO cells by a plasma/albumin free cell culture method and is the active substance in Baxalta's licensed product ADVATE. Thus, the viral safety of BAX 855 is ensured by the octocog alfa (ADVATE) bulk drug substance

manufacturing process as any potential risk of contamination with viruses or adventitious agents during the subsequent manufacturing steps of BAX 855 has been minimized. No substances of animal or human origin are added throughout the entire manufacturing process of BAX 855.

Preclinical studies have demonstrated BAX 855 to have comparable activity and other biochemical properties to ADVATE. The expected prolonged FVIII exposure by BAX 855 was demonstrated in PK studies with a mean residence time (MRT) longer than ADVATE in FVIII knock-out-mice (1.6 fold), rats (1.2 fold) and cynomolgus monkeys (1.5 fold). Prolonged efficacy was shown for BAX 855 in comparison to equivalent doses of ADVATE in 2 primary pharmacodynamic models in FVIII knock-out mice.

Additional data from nonclinical studies can be found in the BAX 855 IB.

6.4.2 Findings from Clinical Studies

A Phase 1, first in human study (Baxter Clinical Study 261101) to assess the safety and PK of BAX 855 in PTPs age 18 to 65 years with severe hemophilia A was conducted in Europe and Japan. The study investigated safety and PK of single doses of 30 and 60 IU/kg BAX 855 compared to the same dose of ADVATE. Subjects were followed for 28 days after BAX 855 administration for safety. Safety assessments included AEs, changes in vital signs, clinical laboratory assessments, and immunogenicity.

A total of 24 subjects were enrolled; 19 were treated and 18 were evaluable for PK analysis. Nine were treated with 30 IU/kg (Cohort 1) and 10 were treated with 60 IU/kg (Cohort 2) of BAX 855, including 2 subjects from Japan.

No subjects developed inhibitors to FVIII or binding antibodies to PEG after BAX 855 infusion. Binding antibodies to FVIII and PEG-FVIII were present in some subjects after BAX 855 infusion but all were at the lowest detectable titers (ie, 1:20 or 1:40); these results could not be analyzed for specificity and were therefore interpreted as “low-titer indeterminate”. Furthermore, no increases in preexisting antibody titers were observed after BAX 855. There were no thrombosis-associated events or allergic reactions. No deaths or other serious adverse events (SAEs) occurred, and none of the 11 non-serious AEs (all mild or moderate) were considered treatment-related. Adverse events reported following BAX 855 administration included vomiting, nasopharyngitis, upper respiratory tract infection, influenza-like illness, arthralgia, headache, and localized swelling. No significant treatment-related changes in laboratory values or vital signs were recorded. There were no notable differences in the type or rate of AEs experienced by subjects after ADVATE infusion versus BAX 855 infusion.

Eighteen subjects (Cohort 1, n=8; Cohort 2, n=10) were evaluable. Based on the 1 stage clotting assay, the median elimination phase half-life ($T_{1/2}$; h) was longer for BAX 855 than for ADVATE in both Cohort 1 (13.60 vs 9.90) and Cohort 2 (16.64 vs 11.11). Other PK parameters also supported an improved PK profile for BAX 855 compared to ADVATE. Refer to the ADVATE IB for more details on the clinical experience to date with ADVATE.

Based on these data, BAX 855 appears to be safe and well tolerated after a single dose administration. The mean $T_{1/2}$ was 1.4 and 1.5-fold higher for BAX 855 compared to ADVATE in Cohorts 1 and 2, respectively, demonstrating prolonged circulation of BAX 855 compared to ADVATE. These data support the use of the BAX 855 dosing regimens planned in this continuation study.

6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

BAX 855 and ADVATE have undergone comparable preclinical single and repeated dose toxicology and pharmacology testing. The results suggest that BAX 855 has a comparable safety profile to ADVATE. Since the core protein of BAX 855 is identical to ADVATE, a safety profile similar to ADVATE is expected for BAX 855 when infused in humans. The most commonly reported adverse drug reactions described for ADVATE in post-marketing clinical studies include: FVIII inhibitors, pyrexia, and headache. Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with ADVATE and have been manifested by dizziness, paresthesia, rash, flushing, face swelling, urticaria, and pruritus. Additional safety experience for ADVATE is provided in the ADVATE IB.

Since BAX 855 is a PEGylated form of ADVATE, it is possible that additional toxicity related to PEG may be observed. BAX 855 may react with preexisting anti-PEG antibodies, resulting in a clinical hypersensitivity reaction. There is also the potential risk of inducing anti-PEG or anti-BAX 855 antibodies following BAX 855 administration. The PEG component of BAX 855 may become dissociated from the FVIII molecule when it is incorporated into tissues. Preclinical studies with other PEGylated drugs have indicated that accumulation can lead to formation of macrophage foam cells, which function to actively remove the PEG molecules. In preclinical studies with other PEGylated drugs, the presence of these “foamy macrophages” has not been associated with any adverse effects.

Binding antibodies against PEG are present in the healthy population and in patients with hemophilia A. BAX 855 may react with pre-existing anti-PEG antibodies, potentially

resulting in a clinical hypersensitivity reaction or increased clearance of BAX 855 from circulation. BAX 855 and ADVATE showed a similar immunogenicity profile in preclinical in vitro and in vivo studies. Data from preclinical studies indicate that PEGylated human FVIII can only induce antibodies against PEG when FVIII is recognized as a foreign protein that can provide immunogenic epitopes for CD4+ T cells. PTPs with a high degree of previous exposure to FVIII should be immunotolerant to FVIII and are considered to have a low risk of developing antibodies against FVIII. Therefore, the risk for PTPs with severe hemophilia A who do not have neutralizing antibodies against FVIII (inhibitors) of developing antibodies against PEG is considered to be rather low when treated with BAX 855. Moreover, results from a tissue cross reactivity study show that even high-affinity antibodies against PEG do not cross-react with any human tissue.

BAX 855 has been administered as a single dose of 30 IU/kg to 9 subjects and a single dose of 60 IU/kg to 10 subjects with severe hemophilia A in a Phase 1 study (Baxter clinical study 261101). Based on data from this study (see Section 6.4.2), there currently are no anticipated risks of BAX 855, beyond those associated with ADVATE, when administered in human subjects.

The comparability of BAX 855 to ADVATE, the preclinical safety profile of BAX 855, and the data from the Phase 1 study, suggest an acceptable risk benefit profile for BAX 855. Additional details related to risks and benefits can be found in the BAX 855 IB.

6.6 Compliance Statement

This study will be conducted in accordance with this protocol, the International Conference on Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is to continue the evaluation of the safety and efficacy of BAX 855 for prophylaxis and treatment of bleeding episodes in adult and pediatric PTPs aged ≤75 years with severe hemophilia A.

7.2 Primary Objectives

The co-primary objectives of the study are:

1. To determine the safety of BAX 855 based on the incidence of FVIII inhibitory antibody development
2. To determine the efficacy of BAX 855 based on the annualized bleed rate (ABR) of spontaneous bleeding episodes

7.3 Secondary Objectives

7.3.1 Efficacy

1. To determine the total ABR (spontaneous and traumatic bleeding episodes)
2. To determine the overall hemostatic efficacy rating of BAX 855 for treatment of breakthrough bleeding episodes
3. To determine the length of intervals between bleeding episodes
4. To characterize the hemostatic efficacy of BAX 855 for treatment of bleeding episodes by the number of BAX 855 infusions for treatment
5. To determine total weight-adjusted consumption of BAX 855 for prophylaxis and for treatment of bleeding episodes
6. To assess Patient Reported Outcomes (PROs) over time for subjects receiving BAX 855

7.3.2 Safety

1. To determine the safety of BAX 855, as assessed by the occurrence of AEs and changes in vital signs and clinical laboratory parameters
2. To determine the immunogenicity of BAX 855

7.4 Exploratory Objectives

1. To assess patient satisfaction, patient activity levels, and health resource use over time for subjects receiving BAX 855
2. To determine the potential correlation between TGA parameters, FVIII trough levels and ABR

8. STUDY DESIGN

8.1 Brief Summary

This is a phase 3b, prospective, open label, multi-center study to evaluate the safety and efficacy of BAX 855 for prophylactic use and the control of bleeding episodes in approximately 200 pediatric and adult PTPs ≤75 years of age with severe hemophilia A.

The study plans to include subjects from other BAX 855 studies and BAX 855-naïve subjects.

Subjects will receive either a fixed dose prophylaxis with BAX 855 consisting of 45 ± 5 IU/kg for subjects aged ≥ 12 years or 50 ± 10 IU/kg for subjects aged < 12 years twice weekly or, subjects can decide to receive a PK-tailored prophylactic BAX 855 dosing regimen based on the subject's individual PK to maintain FVIII trough levels of ≥3%.

Subjects will be treated on the specified prophylactic treatment regimen until they reach at least 100 EDs (as accumulated across all BAX 855 studies). The overall study design is illustrated in Figure 1.

8.2 Overall Study Design

Subjects who complete treatment and assessments in the other BAX 855 studies and BAX 855-naïve subjects who fulfill the inclusion/exclusion criteria will be eligible to participate in this continuation study. Approximately 250 PTPs with severe hemophilia A will be enrolled to achieve 200 evaluable subjects. This study was designed to be in compliance with EMA/CHMP/BPWP/144533/2009[6] recommendations for the study of FVIII in severe hemophilia A.

The subject's hemophilia history, bleeding episode history, and FVIII usage and treatment regimen(s) within the previous year will be collected at screening for BAX 855 naïve subjects. Results of the screening assessments will be used to establish subject's eligibility for this study and may serve as baseline measurements. Subjects transitioning from the other BAX 855 studies may use end of study assessments in their prior study for screening assessments in this continuation study.

Once eligibility is established, subjects can choose to receive either a fixed BAX 855 prophylaxis or a PK-tailored BAX 855 prophylaxis (as described in Section 8.7.3). Subjects will also treat breakthrough bleeding episodes with BAX 855. Details on bleeding episodes, the number of infusions used for treatment, and the efficacy of treatment (based on a 4-point rating scale; see Section 11.2) will be recorded in an electronic diary (e-diary). Subjects will be treated with BAX 855 for a minimum of 100 EDs (accumulated across all BAX 855 studies they have participated in).

Transitioning subjects receiving a fixed dose prophylactic treatment regimen will return to the study site at 6 weeks following screening to confirm eligibility and at this visit and subsequent visits every 3 months following screening, IR will be determined, efficacy and safety will be assessed and e-diary will be reviewed. BAX855 naïve subjects with

confirmed eligibility will undergo their baseline visit for determination of IR at exposure day 1 (ED1) and return to the study site after 6 weeks and every 3 months following their baseline visit for IR determination, efficacy and safety assessment and e-diary review.

Subjects receiving a PK-tailored prophylactic treatment regimen will have their PK assessment performed following eligibility confirmation. Following PK assessment, they undergo their baseline visit and subsequent visits every 3 months following their baseline visit for IR determination, efficacy and safety assessment and e-diary review. In addition, at 4 ,8 and 18 weeks after the baseline visit, subjects' FVIII levels, TGA parameters and VWF antigen will be measured to ensure that FVIII trough levels of ≥3% are maintained, and, if necessary, dose adjustments will have to be performed. Also, hemostatic efficacy and clinical safety will be assessed and e-diary reviewed.

Investigators will review e-diaries for untoward events, concomitant medications, non-drug therapies, and patient reported outcomes (PROs; see Section 10.5.2). Safety assessments performed at the study visit will include immunogenicity (inhibitory antibodies for FVIII and binding antibodies for FVIII, BAX 855, PEG, and CHO), and changes in conditions of the physical examination, vital signs, and clinical laboratory assessments (hematology, clinical chemistry, and lipids). Subjects who develop a high responder inhibitor (> 5 Bethesda Units [BU]), or who develop a low responder inhibitor (≤ 5 BU but ≥ 0.6 BU) that cannot be adequately managed by the prescribed prophylaxis regimen with BAX 855 will be discontinued from study. At every study visit[iii], IR for FVIII activity and TGA parameters (optional in subjects receiving fixed dose prophylaxis) will be determined within 30 minutes prior to infusion with 60 ± 5 IU/kg BAX 855 and 30 ± 15 minutes following the infusion. Also, TGA parameters and pre-infusion VWF antigen level will be assessed in subjects receiving a PK-tailored dosing (optional for subjects aged < 12 years).

The sponsor will suspend enrollment and treatment if 2 or more subjects develop anaphylaxis after BAX 855 treatment. The sponsor may stop this study at any time. In addition, the sponsor may modify the study based on results of the other BAX 855 studies.

8.3 Duration of Study Period(s) and Subject Participation

The overall duration of this continuation study is estimated to be approximately 4 years from study initiation (ie, first subject enrolled by signing informed consent) to study

[iii] Except at visits 4 ± 1, 8 ± 1 and 18 ± 2 weeks following baseline in those subjects receiving PK-tailored treatment regimen.

completion (ie, last subject last visit). Recruitment of transitioning subjects will continue until the last subject has completed any other BAX 855 study.

Each subject will participate in the study until a total of at least 100 EDs to BAX 855 has been achieved (accumulated across all BAX 855 studies in which each subject participated). Depending on the subject's BAX 855 exposure history and treatment regimen given, the planned duration of subject participation to reach the 100 EDs (from enrollment to subject completion) can vary from approximately 3 to 12 months. However, extension of the study duration for individual subjects beyond the 100 EDs may be granted.

8.4 Outcome Measures

8.4.1 Primary Outcome Measures

8.4.1.1 Safety

- Development of inhibitory antibodies to FVIII

8.4.1.2 Efficacy

- Spontaneous ABR

8.4.2 Secondary Outcome Measures

8.4.2.1 Efficacy

1. Total ABR (spontaneous and traumatic bleeding episodes)
2. Overall hemostatic efficacy rating of BAX 855 for treatment of breakthrough bleeding episodes
3. Number of BAX 855 infusions to treat bleeding episodes
4. Time intervals between bleeding episodes
5. Weight-adjusted consumption of BAX 855

8.4.2.2 Safety

1. Occurrence of AEs and SAEs
2. Changes in vital signs and clinical laboratory parameters (hematology, clinical chemistry, and lipids)
3. Immunogenicity
    a. Binding antibodies (IgG and IgM) to FVIII, BAX 855, and PEG
    b. Anti-CHO antibodies

8.4.2.3 Patient Reported Outcomes

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

1. Bleed and pain severity as measured using the Haemo-SYM questionnaire
2. HRQoL as assessed using the SF-36/PedsQL questionnaires

8.4.3 Exploratory Outcomes Measure

1. Patient satisfaction with treatment will be assessed using the Satisfaction Question Set
2. Patient Activity Level
3. Health resource use data (eg, physician office visits, hospitalizations, days missed from work/school)
4. TGA parameters, FVIII trough levels and ABR

8.5 Randomization and Blinding

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

8.6 Study Stopping Rules

This study will be stopped if 1 or more of the following criteria are met:

Enrollment and treatment in this continuation study will be suspended or stopped, if the following criterion is met:

1. If 2 or more subjects develop anaphylaxis following exposure to BAX 855

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

1. The sponsor decides to terminate the study based upon its own assessment of safety
2. The sponsor decides to terminate the study for administrative reasons

8.7 Investigational Product(s)

8.7.1 Packaging, Labeling, and Storage

BAX 855 is formulated as a sterile, highly purified protein preparation in lyophilized form for i.v. infusion and is provided in single-dose vials along with a vial of diluent (2 or 5 mL SWFI, as available). A butterfly transfer set with luer-lock syringes and a needleless transfer device will be used for reconstitution and bolus i.v. delivery (BAXJECT II high-flow [HF] and BAXJECT III, as available). The BAXJECT system is a needleless liquid transfer device with the primary function of transferring diluent from

its vial into an evacuated vial containing product requiring reconstitution prior to infusion.

A minimum of 4 lots of BAX 855 manufactured for this study will be used. Four nominal potencies of BAX 855 will be used, depending upon availability: 250, 500, 1,000 and 2,000 IU/vial.

The recommended storage conditions for BAX 855 are 2°C to 8°C (36°F to 46°F) and it should not be allowed to freeze. BAX 855 should be stored and protected from light. The reconstituted product should ideally be used immediately but no longer than 3 hours after reconstitution.

For additional information, such as reconstitution instructions, refer to the BAX 855 IB and/or other specific instructions provided by the sponsor.

8.7.2 Administration

Following reconstitution, BAX 855 should be administered using plastic syringes provided by the sponsor since proteins such as BAX 855 may adhere to the surface of glass syringes. BAX 855 will be administered i.v., using an appropriately sized syringe, as a bolus infusion over a period of ≤5 minutes with a maximum infusion rate of 10 mL/min, as described in the BAX 855 IB. The reconstituted BAX 855 must be administered at room temperature and within 3 hours.

BAX 855 dose calculation will be based on the stated actual potency on vials in respective lots.

PK assessment and determination of IR

For the PK assessment in individual subjects, only vials of the same lot with a nominal potency of 500 IU should preferably be used. Alternatively, 1000 IU vials of the same lot could be used.

- In subjects aged ≥ 12 years: total calculated dose may be rounded up to the nearest whole vial in case 500 IU potency vials are used. However, in case vials with a nominal potency of 1,000 IU/vial are used, the total calculated dose should not be rounded up to the nearest whole vial to ensure accurate dosing (eg, 2.5 vials).
- In subjects aged < 12 years: The exact amount of IUs has to be administered irrespective of the potency used (eg, 1.5 vials).

Infusions for prophylaxis and treatment of bleeding episodes

Two different lots per infusion may be used, however, each vial must be reconstituted with its own kit. The total calculated dose can be rounded up to the nearest whole vial.

8.7.3 Description of Treatment

Subjects will be treated on either a fixed dose or PK-tailored prophylactic treatment regimen[iv] until they reach at least 100 EDs (accumulated across all studies). Subjects who received on-demand treatment in the pivotal study (Study 261201) and decide to receive a PK-tailored treatment regimen in this study will first receive a fixed dose prophylactic treatment regimen (as outlined in Section 8.7.3.1) until their dose and frequency is determined and the first PK-tailored dose administered.

8.7.3.1 Fixed Dose Prophylactic Treatment Regimen

The fixed dose prophylactic treatment regimen with BAX 855 will be age-dependent as follows:

- Subjects aged ≥ 12 years: 45 ± 5 IU/kg twice weekly, which may be increased up to 80 IU/kg
- Subjects aged < 12 years: 50 ± 10 IU/kg twice weekly, which may be increased up to 80 IU/kg

Subjects must adhere as closely as possible to the dosing regimen. The days of the week on which treatment is administered may be selected by the subject and/or his/her physician and should be selected to provide maximum coverage for vigorous activities. Dosing must be administered twice weekly, at 3 and 4 day intervals (Option X), or 3.5 day intervals (Option Y with AM and PM dosing) and should be maintained during the study (Table 2). If a dose is missed, it must be documented and the next dose will be taken as soon as possible. After this dose, the regularly scheduled regimen will be resumed. For example, in Option X, if twice weekly dosing is scheduled for every Monday and Thursday and the subject misses the Thursday dose, he/she should infuse the next dose on Friday and then resume his/her schedule with subsequent dose on Monday). And for Option Y, if dosing is scheduled for the morning on Monday and the evening dose on Thursday, and the subject misses the Thursday dose, he/she should infuse the

iv Please note that subjects who are on a 30-80 IU/kg every 5 days (q5d) or every 7 days (q7d) treatment regimen prior to this protocol amendment 4 (dated 23 May 2014) being effective can decide to continue on their 30-80 IU/kg q5d or q7d treatment regimen after this protocol amendment 4 (dated 23 May 2014) is effective. These subjects will then follow the procedures as described for transitioning subjects on a fixed dose prophylactic treatment regimen (see also Supplement 20.3.1). Additionally, these subjects can decide to switch to a fixed dose or PK-tailored prophylactic treatment regimen as per protocol amendment 4 (dated 23 May 2014) at any time during the study.

next dose on Friday morning, and then resume his/her schedule with a subsequent dose on Monday morning.

Table 2
BAX 855 Example Dosing Frequency

Day	Mon	Tue	Wed	Thu	Fri	Sat	Sun
Morning	X or Y			X			
Evening				Y			

Subjects requiring treatment for a breakthrough bleeding episode should resume prophylaxis as soon as the bleeding episode is resolved. They should return to the same schedule of dosing as if prophylactic dosing was not interrupted. For example, if the subject is typically dosed every Monday and Thursday and is treated for a bleeding episode on Wednesday and the bleeding episode is resolved on Thursday, he/she would resume prophylaxis on Thursday; if the bleeding episode is not resolved until Friday, his/her next prophylactic dose would be on Monday (ie, subjects will resume their prophylactic treatment regimen the next scheduled day after the last therapeutic infusion for the treatment of a bleeding episode).

In order to ensure the required washout periods of at least 84 to preferably 96 hours prior to study visits, the scheduled regimen may be interrupted for this period but should be resumed once the study visit is completed.

8.7.3.2 BAX 855 Dose and/or Frequency Adjustments for Subjects on Fixed Dose Prophylactic Treatment Regimen

Subjects meeting any of the following criteria during their fixed dose prophylaxis may have their BAX 855 dosage and/or infusion frequency increased:

- Two or more spontaneous (not trauma-related) bleeding episodes in the same target joint within any 2-month period
- One or more spontaneous (not trauma-related) bleeding episodes in a non-target joint within any 2-month period
- FVIII trough level < 1% and investigator's estimate that the subject has an increased risk of bleeding

The BAX 855 dosage may be increased gradually up to a maximum of 80 ± 5 IU/kg and/or an increase in frequency may be considered if deemed necessary, in case the

subject continues to experience spontaneous breakthrough bleeding episodes. In any case, the sponsor should be notified if any of the above criteria are met and dose adjustment is performed.

Additionally, for subjects with severe hemophilic arthropathy and/or target joints who continue to experience recurrent bleeding episodes despite adjustments to the prophylactic dose and/or dosing frequency, an ultrasound of the affected joint(s) should be performed to verify the presence of a bleed.

8.7.3.3 PK-Tailored Prophylactic Treatment Regimen

Subjects may decide to receive a PK-tailored prophylactic treatment regimen to maintain a FVIII trough level of ≥3%. The dose should not exceed 80 IU/kg and the FVIII peak levels should not exceed 200%.

Subjects choosing a PK-tailored prophylactic treatment who did not undergo a PK assessment in a previous BAX 855 study will undergo an abbreviated PK assessment with 1 pre- and 6 post-infusion sampling times up to 96 ± 4 hours (for subjects aged ≥ 12 years) or 1 pre- and 3 post-infusion sampling times up to 56 ± 4 hours (for subjects aged < 12 years) following the infusion of 60 ± 5 IU/kg of BAX 855.

Based on the subject's individual PK, the dose will be calculated to ensure FVIII target trough levels in plasma of ≥3%. The dose will be calculated by the sponsor and provided to the study site. The frequency of dosing will be at least twice weekly or more, depending on subject's $T_{1/2}$ and preference for treatment schedule.

Subjects must adhere as closely as possible to the dosing regimen. If a dose is missed, it must be documented and the next dose will be taken as soon as possible. After this dose, the regularly scheduled regimen will be resumed. Subjects requiring treatment for a breakthrough bleeding episode should resume their PK-tailored prophylaxis as soon as the bleeding episode is resolved.

In order to ensure the required washout periods of at least 84 to preferably 96 hours prior to study visits[v], the scheduled regimen may be interrupted for this period but should be resumed once the study visit is completed. For the determination of FVIII trough levels at visit 4 ± 1, 8 ± 1 and 18 ± 2 weeks following baseline, no wash-out period is required. The visits should be planned so that a blood sample can be drawn immediately prior to a regularly planned prophylactic infusion.

v For subjects on a more than twice weekly dosing regimen, every attempt should be made to adhere to the minimum washout period of 84 hours.

8.7.3.4 BAX 855 Dose and/or Frequency Adjustments for Subjects on PK-Tailored Prophylactic Treatment Regimen

Subjects meeting any of the following criteria during their PK-tailored prophylaxis may have their BAX 855 dosage and/or infusion frequency increased:

- Two or more spontaneous (not trauma-related) bleeding episodes in the same target joint within any 2-month period
- One or more spontaneous (not trauma-related) bleeding episodes in a non-target joint within any 2-month period
- FVIII trough level < 3%

The BAX 855 dosage may be increased gradually up to a maximum of 80 ± 5 IU/kg and/or the dosing frequency may be increased, in case the subject continues to experience spontaneous breakthrough bleeding episodes. In any case, the sponsor should be notified if any of the above criteria are met and dose/frequency adjustment is performed; dose/frequency adjustment options can be discussed with the sponsor's medical director.

Additionally, subjects with severe hemophilic arthropathy and/or target joints who continue to experience recurrent bleeding episodes despite adjustments to the prophylactic dose and/or dosing frequency, an ultrasound of the affected joint(s) should be performed to verify the presence of a bleed.

8.7.3.5 Treatment of Bleeding Episodes

BAX 855 will be used for the treatment of bleeding episodes (ie, breakthrough bleeding episodes during prophylaxis), according to the guidelines outlined in Table 3. These guidelines may be adjusted (ie, below 10 [± 5] IU/kg or above 60 [± 5] IU/kg) by the investigator based upon his or her clinical judgment and the severity of the bleeding episode (see Table 3).

It is critical that treatment of a bleed is initiated as soon as possible after occurrence of the bleeding episode.

When bleeding is controlled, additional infusions of BAX 855 to maintain hemostasis is permitted, if required. The infusion for maintenance of hemostasis should be administered within 24 hours of the most recent infusion. Otherwise it is considered a prophylactic infusion.

Table 3
BAX 855 Treatment Guidelines for Bleeding Episodes

Type of Bleeding Episode	FVIII Level Required (%) *Dose (IU/kg)*	Frequency of Dosing
Minor Early hemarthrosis, mild muscle bleeding, or mild oral bleeding, including, epistaxis	20 to 40% *Dose 10 to 20 (±5) IU/kg*	Repeat infusions every 12 to 24 h. Duration: at least 1 day, until the bleeding episode is resolved or healing is achieved
Moderate Moderate bleeding into muscles, bleeding into the oral cavity, definite/more extensive hemarthroses, and known trauma	30 to 60% *Dose 15 to 30 (±5) IU/kg*	Repeat infusions every 12 to 24 h for 3 days or more until the pain and acute disability/incapacity are resolved
Major Significant gastrointestinal bleeding, intracranial, intra-abdominal, or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces or iliopsoas sheath, fractures, head trauma	60 to 100% *Dose 30 to 60 (±5) IU/kg* In case of life-threatening bleeds, a dose of 80 (±5) IU/kg may be considered	Repeat infusions every 8 to 12 h until the bleeding episode/threat is resolved

The required units will be calculated according to the following formula:

body weight (kg) x desired FVIII rise (%) (IU/dL) x {reciprocal of observed recovery}

Whenever possible, the subject's most recent individual IR should be used. In its absence, an anticipated recovery of 2.5 (IU/dL)/(IU/kg) based on data of the Phase 1 study, Cohort 2, should be assumed and the required units calculated using the following formula:

body weight (kg) x desired FIX rise (%or (IU/dL) x 0.4 dL/kg

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. In subjects with severe hemophilic arthropathy and/or target joints with recurrent bleeding requiring more than 2 infusions per bleeding and/or where efficacy ratings are generally fair or none, an ultrasound of the affected joint(s) may be considered to verify the presence of a bleed.

8.7.3.6 Immune Tolerance Induction for Inhibitor Development

Subjects who develop a confirmed (ie, 2 separate assessments within a 2 to 4 week period from the central laboratory) high responder inhibitor (>5 BU) or low responder inhibitor (≤5 BU but ≥0.6 BU) that cannot be adequately managed by the protocol-required prophylactic regimen with BAX 855 will be discontinued from this continuation study. The decision to initiate immune tolerance induction (ITI) (ITI) with ADVATE will be made by the subject's physician, and may be discussed with the sponsor's medical director prior to initiation. The regimen used for ITI will be determined by the treating physician but must be approved by the sponsor's medical director. ITI is not within the scope of this study.

8.7.4 Treatment for Surgery or Dental Procedures

Subjects enrolled in this continuation study who require elective major or minor surgical or dental procedures or minor emergency surgical or dental procedures may be eligible to enroll in the BAX 855 surgery study (Study 261204), which is evaluating efficacy and safety of BAX 855 for perioperative management, if the study is open for enrollment. Exemptions may be granted for minor interventions in case the surgery study is not in place at the study site and the intervention can be managed by one prophylactic infusion and an additional infusion to maintain hemostasis. However, to ensure an adequate dose, at least an individual IR must be available which can also be based on FVIII activity levels determined at the local laboratory with back-up samples drawn for determination at the central laboratory. Any required major emergency surgery will result in withdrawal of the subject.

Upon completion of the surgery study, subjects may be eligible to return to this continuation study when they are able to resume their continuation study-specific prophylaxis regimen and with the approval of the sponsor's medical director. Upon return to this study, these subjects will receive their previous continuation study treatment regimen.

Subjects from this continuation study who participate in the surgery study will continue to receive their study-specific BAX 855 treatment from the continuation study as follows:

- For subjects undergoing PK (required for major surgery) or IR (required for minor surgery) assessment in the surgery study:

1. From signing the informed consent until the pre-surgical PK[vi]/IR[vii] assessment required for major surgery.
2. From completion of the pre-surgical PK/IR assessment until the loading dose prior to surgery.

- For subjects not undergoing PK/IR assessment in the surgery study:

1. From signing the informed consent until the loading dose prior to surgery.

During the period from screening up to the loading dose prior to the surgery in which subjects receive BAX 855 from the continuation study, subjects will maintain their e-diaries for the continuation study, and the investigator of the continuation study will be responsible for the subject's safety and treatment. Any data collected during the above-listed periods will be recorded as part of this continuation study.

During the pre-surgery PK assessment and during the period starting with the initial loading dose until the end of the surgery study, subjects will receive BAX 855 from the surgery study. Any data collected during these periods will be recorded as part of the surgery study.

EDs will be counted in the subjects' primary study, ie BAX 855 EDs accumulated as part of the surgery study will also be factored into the total number of EDs in the continuation study.

For subjects transitioning back from the surgery study to this study, the investigator will determine whether the subject continues to meet the eligibility criteria using end of study data from the surgery study.

8.7.5 . Investigational Product Accountability

The investigator will ensure that the IP is stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and

vi Subjects undergoing major surgeries who have undergone a PK determination in the current study do not require a pre-surgical PK assessment.

vii Subjects undergoing minor surgeries but do not have an IR performed within 3 months of surgery have to perform an IR.

disposition. IP must be dispensed only at the study site or other suitable location (eg, infusion center, home, as applicable per study design). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP will be returned to the study site, which will then return it to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

For further detail, please refer to the pharmacy and IP distribution manual for this study.

8.8 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

For additional information on study documentation and electronic case report forms (eCRFs), see Section 17.2. The use of subject diaries is described in Section 10.5.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

9.1.1 Subjects Transitioning from Other BAX 855 Studies

Subjects transitioning from other BAX 855 studies can be provided with the continuation study informed consent form (ICF) prior to the end of study visit to review and consider participation in this continuation study. These subjects will complete any additional screening assessments within 2 weeks of the previous study's end of study visit and will return to the study site within 6 (± 1) weeks of the previous study end of study visit to confirm eligibility for this continuation study.

Subjects transitioning from other BAX 855 studies who meet **ALL** of the following criteria are eligible for this study:

1. Subject has completed a previous BAX 855 study and is willing to immediately transition into this continuation study.[viii]
2. Subject is ≤75 years of age at screening of the previous BAX 855 study.
3. Subject continues to have a Karnofsky (for subjects aged ≥ 16 years) or Lansky (for subjects aged < 16 years) performance score of ≥ 60 (see Section 20.5).
4. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm^3, as confirmed by central laboratory at screening.
5. Subject is hepatitis C virus negative (HCV-) by antibody or PCR testing (if positive, antibody titer will be confirmed by PCR), as confirmed by central laboratory at screening; or HCV+ with chronic stable hepatitis.
6. If female of childbearing potential, subject presents with a negative urine pregnancy test and agrees to employ adequate birth control measures for the duration of the study.
7. Subject and/or legally authorized representative is willing and able to comply with the requirements of the protocol.

9.1.2 BAX 855 Naïve Subjects

BAX 855 naïve subjects who are ≥ 12 years of age can only be enrolled in this continuation study after enrollment in the phase 2/3 pivotal study is closed. BAX 855 naïve subjects who are < 12 years of age can only be enrolled in this continuation study after enrollment in the pediatric PTP study is closed.

Enrolment of BAX 855 naïve subjects will only start once the sponsor has notified the study sites accordingly.

BAX 855 naïve subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject is ≤75 years of age at screening.
2. Subject is naïve to BAX 855.

viii NOTE: Subjects who have received FVIII concentrates other than BAX 855 following completion of the previous BAX 855 study are excluded from participation in this continuation study.

3. Subject has severe hemophilia A (FVIII clotting activity < 1%) as confirmed by central laboratory at screening after at least a 72-hour washout period[ix].
4. Subject aged ≥ 6 years has documented previous treatment with plasma-derived FVIII or rFVIII for ≥ 150 EDs.
5. Subject aged < 6 years has documented previous treatment with plasma-derived FVIII concentrates or rFVIII for ≥ 50 EDs.
6. Subject is currently receiving prophylaxis or on-demand therapy with FVIII.
7. Subject has a Karnofsky (for subjects aged ≥ 16 years) or Lansky (for subjects aged < 16 years) performance score of ≥ 60 (see Section 20.5).
8. Subject is HIV-; or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm^3, as confirmed by central laboratory at screening.
9. Subject is HCV- by antibody or PCR testing (if positive, antibody titer will be confirmed by PCR), as confirmed by central laboratory at screening; or HCV+ with chronic stable hepatitis.
10. If female of childbearing potential, subject presents with a negative urine pregnancy test and agrees to employ adequate birth control measures for the duration of the study.
11. Subject and/or legally authorized representative is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

9.2.1 Subjects Transitioning from Other BAX 855 Studies

Subjects transitioning from other BAX 855 studies who meet **ANY** of the following criteria are not eligible for this study:

1. Subject had detectable FVIII inhibitory antibodies (≥ 0.6 BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening.
2. Subject has developed FVIII inhibitory antibodies (≥ 0.6 BU using the Nijmegen modification of the Bethesda assay as determined at central laboratory in a previous BAX 855 study).
3. Subject has acquired a hemostatic defect other than hemophilia A (eg, qualitative platelet defect or von Willebrand's disease) in a previous BAX 855 study.

ix If FVIII activity is ≥1%, severe hemophilia A classification can be confirmed by historically documented FVIII clotting activity < 1% performed by a certified clinical laboratory or by a documented genotype known to result in severe hemophilia A.

4. Subject has severe chronic hepatic dysfunction (eg, ≥ 5 times upper limit of normal alanine aminotransferase [ALT], as confirmed by central laboratory at screening).
5. Subject has severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening.
6. Subject experienced a life-threatening or gastrointestinal bleeding episode within 3 months prior to study entry.
7. Subject is scheduled to use other PEGylated drugs during study participation.
8. Subject is planning to take part in any other clinical study during the course of the continuation study, with the exception of any other parallel BAX 855 study.
9. Subject has medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance.
10. Subject is a family member or employee of the investigator.

9.2.2 BAX 855 Naïve Subjects

BAX 855 naïve subjects who meet **ANY** of the following criteria are not eligible for this study:

1. Subject has detectable FVIII inhibitory antibodies (≥ 0.6 BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening.
2. Subject has 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.
3. Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (eg, qualitative platelet defect or von Willebrand's disease).
4. Subject has known hypersensitivity towards mouse or hamster proteins, PEG, or Tween 80.
5. Subject has severe chronic hepatic dysfunction eg, ≥ 5 times upper limit of normal ALT, as confirmed by central laboratory at screening).
6. Subject has severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening.
7. Subject experienced a life-threatening or gastrointestinal bleeding episode within 3 months prior to study entry.
8. Subject has current or recent (< 30 days) use of other PEGylated drugs prior to study participation or scheduled use of such drugs during study participation.

9. Subject has participated in another clinical study involving an IP other than BAX 855 or 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.
10. Subject has medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance.
11. Subject is a family member or employee of the investigator.

9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (ie, reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study eCRF. Assessments to be performed at the end of study visit (including in cases of withdrawal or discontinuation) are described in Section 10.6 and Section 20.3.

Discontinuation (ie, complete withdrawal from study participation) may be due to dropout (ie, active discontinuation by subject) or loss to follow-up (ie, discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also may be withdrawn from treatment or discontinued from further study participation for the following reasons:

- The subject develops a confirmed high responder inhibitory antibody to FVIII (>5 BU by Nijmegen modification of the Bethesda assay) or a low responder inhibitory antibody (≤5 BU but ≥0.6 BU) that cannot be managed by the protocol-required treatment.
- The subject experiences a severe anaphylactic reaction to BAX 855.
- The subject requires therapy with another PEGylated product (eg, PEG-Interferon).
- The subject frequently misses administration of IP (ie, misses more than 30% of planned prophylactic doses within any 3-month period).
- The subject is non-compliant with study procedures, in the opinion of the investigator.

- The subject repeatedly uses another FVIII therapy for prophylaxis (in the absence of an acceptable justification to the sponsor) or for the treatment of bleeding episodes.
- The subject requires a surgical or dental procedure and is not eligible or does not consent for the surgery study, or participates in the surgery study and then refuses to resume participation in this continuation study. If the surgery study is closed, the subject will be withdrawn from the continuation study.
- The subject experiences a life-threatening bleeding episode (eg, any gastrointestinal hemorrhage or intracranial hemorrhage).
- The subject experiences severe trauma or requires emergency surgery with FVIII replacement therapy other than BAX 855.
- The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year post-delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient and/or patient's legally authorized representative who provides informed consent and, as appropriate, any patient who provides assent (ie, signs and dates the informed consent form and assent form, if applicable) is considered enrolled in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (eg, 261203) to be provided by the sponsor, a 3-digit number study site number (eg, 002) to be provided by the sponsor, and 3-digit subject number (eg, 003) reflecting the order of enrollment (ie, signing the informed consent form). For example, the third subject who signed an informed consent form at study site 002 will be identified as Subject 261203-002003. All study documents (eg, eCRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (eg, collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. If

a subject does not satisfy all screening criteria, the same subject may be re-screened at a later date. A complete or partial re-screen may also become necessary at the discretion of the investigator or sponsor. All screening data will be collected and reported in eCRFs, regardless of screening outcome. For the purpose of analysis, only the data from the most recent screening visit will be used. If a subject is re-screened, the End of Study eCRF should be completed, and a new ICF, new SIC and new eCRF are required for that subject. The screening procedures including laboratory evaluations must be completed within 45 days or repeated if more than 45 days have elapsed. Exemptions may be granted for administrative reasons, eg delay in timely availability of laboratory results.

The overall study design is illustrated in the Figure 1. A flow diagram of required procedures is presented in Supplement 20.2. Details on the procedures to be performed at each study visit, including screening, can be found in Supplement 20.3 Schedule of Study Procedures and Assessments and Supplement 20.4 Clinical Laboratory Assessments.

10.3.1 Subjects Transitioning from Other BAX 855 Studies

Subjects transitioning from other BAX 855 studies can use the end of study assessments in their previous BAX 855 study for screening visit assessments in this continuation study. Any additional required screening assessments will be performed the same day. Subjects will return to the study site no later than 6 (± 1) weeks after the end of study visit in their prior study/continuation study's screening visit to confirm eligibility.

Additionally, transitioning subjects will receive IP treatment either as part of the IR determination of the end of study visit of the previous BAX855 study or the first IP treatment will be given at the screening visit of this continuation study to subjects transitioning from other BAX 855 studies.

Transitioning subjects[x] who decide to receive a PK-tailored treatment regimen will continue receiving their study-specific treatment regimen with BAX 855[xi] (eg, twice weekly 45 ± 5 IU/kg) until baseline/start of PK-tailored prophylaxis. The study-specific prophylactic treatment regimen will be interrupted by one infusion for PK determination in those subjects for whom PK is not yet available.

x As well as subjects who are already participating in the continuation study.
xi NOTE: This refers to the type of treatment that subjects will receive with BAX 855 from this continuation study (not from the previous BAX 855 study).

10.3.2 BAX 855 Naïve Subjects

BAX 855 naïve subjects will continue using their FVIII concentrate and treatment regimen until baseline/start of prophylaxis, except for one infusion with BAX 855 for PK determination (for subjects receiving a PK-tailored prophylactic treatment regimen).

10.4 Medications and Non-Drug Therapies

The following medications are **not** permitted within 30 days before study entry and during the course of the study:

- Any PEGylated medication (eg, PEG-interferon)
- Any investigational drug, biologic, or device, except BAX 855 in case of transitioning subjects

A subject who has taken any of these medications will be considered a protocol deviation.

The use of any FVIII concentrate other than BAX 855 during the course of the study following the first BAX 855 infusion[xii] will result in the immediate withdrawal of the subject. Every effort should be made to have the Completion/Termination Visit performed. The use of (commercial) ADVATE may be permitted for a short period of time for administrative reasons.

The following medications and non-drug therapies are permitted before study entry and during the course of the study:

- Medications:
  - Hemostatic agents, such as tranexamic acid, are permitted, as indicated by the subject's treating physician, to treat mucosal bleeding during the study
  - Any medications deemed necessary by the subject's physician to treat or prevent any medical condition
  - Any over-the-counter medication used by the subject to treat symptoms or signs
  - Supplemental vitamins, minerals
- Non-drug therapies:
  - Any non-drug therapy (eg, physiotherapy) deemed necessary by the subject's physician to treat or prevent any medical condition

[xii] This infusion may be the first prophylactic infusion or infusion for the determination of IR for FVIII activity.

10.5 Subject Diary and Patient Reported Outcomes

10.5.1 Subject Diary

An electronic subject diary will be provided to each subject at the screening visit to record the following information:

1. Infusion record for BAX 855
2. Details of bleeding episodes and response to treatment
3. Untoward events
4. Concomitant medications (including immunizations) and non-drug therapies
5. Patient Reported Outcomes (PROs)

For each bleeding episode, the following information will be recorded by the subject/subject's caregiver or by authorized, qualified personnel at the study site:

- Location of bleed, eg, joint, soft tissue, muscle, body cavity, intracranial, other.
- Type of bleed, ie, spontaneous (definitely no injury/trauma), injury (definitely due to injury/trauma), or unknown (pediatric subject was not observed by an adult to reliably determine and verify whether it was spontaneous or injury-related).
- Severity of bleed, eg, minor, moderate, major (see Table 3).
- Date and time of onset of bleed.
- Date and time of each infusion of BAX 855 required to achieve adequate hemostasis.
- Date and time of resolution of bleeding episode.
- Overall clinical efficacy rating according to the rating scale as described in Table 4 at 24 (±2) hours after initiation of treatment and at resolution of bleed.

Details pertaining to all treatments for each bleed, including response to treatment, will be recorded by study subjects/subjects' caregiver in subject diaries provided by the sponsor or sponsor's representative.

AEs and the details of concomitant medication used coincident with the treatment of all acute bleeding episodes will be recorded.

NOTE: Bleeding episodes are not to be reported as AEs (Section 12.3).

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request

missing information periodically and in a timely manner. Untoward events recorded in the diary will be reported as AEs according to the investigator's discretion and clinical judgment.

Subject entries in the diary will serve as source records. During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the eCRF by a validated transfer.

PROs will be administered at the start of prophylaxis treatment (baseline), every 6 months and at the end of study visit. Some questionnaires may not be administered in all participating countries due to the unavailability of linguistically validated translations for certain PRO measures in some countries. In addition, subjects who are younger than the minimal age limit required for these assessments will not complete the assessments.

10.5.2 Patient Reported Outcomes

The following PROs will be assessed at the start of prophylaxis treatment, every 6 months and at the end of study visit:

- Bleed and pain severity will be measured using the Haemo-SYM for subjects ≥ 18 years of age
- HRQoL will be assessed using the Short Form 36 (SF-36) for subjects ≥ 14 years of age
- HRQoL will be assessed using the Pediatric Quality of Life Inventory™ (PedsQL[xiii]) for subjects < 14 years of age (for subjects aged ≥ 8 to < 14 years, the PedsQL Child report (23 items) will be completed; for subjects aged ≥ 5 to < 8 years, the PedsQL Parent report (23 items) will be completed; for subjects aged ≥2 and < 5 years, the PedsQL Parent report (21 items) will be completed; for subjects aged < 2 years, the PedsQL is not used)
- Patient satisfaction with treatment will be assessed using the Satisfaction Questionnaire (for subjects aged ≥ 12 years, the subject completes the questionnaire; for subjects aged < 12 years, the caregiver completes it on behalf of the subject)
- Patient Activity Level (for subjects aged ≥ 12 years, the subject completes the assessment; for subjects aged < 12 years, the caregiver completes it on behalf of the subject)

xiii NOTE: Patients should be given the same questionnaire at follow-up that they were given at baseline, even if they move up an age range during the study.

Details on each of the PROs are as follows:

- **Haemo-SYM Questionnaire** – This is a self-administered, validated questionnaire designed to assess symptom severity in patients with hemophilia. This measure contains 17 items and includes 2 domains: Bleeds and Pain. Scores for each of these 2 domains can be calculated, with higher scores indicating more severe symptoms.
- **SF-36** – The SF-36 is a self-administered, validated questionnaire designed to measure generic HRQoL. This 36-item questionnaire measures 8 domains, including: Physical functioning, Role-physical, Bodily pain, General health, Vitality, Social functioning, Role emotional, and Mental health. Two summary scores can be calculated, the Physical Component Score, and the Mental Component Score. Additionally, scores can be calculated for each of the 8 domains. Higher scores indicate better health status.
- **PedsQL** – The PedsQL is a generic HRQoL instrument designed specifically for a pediatric population. Depending on the subject's age, the PedsQL contains 23 (for subjects aged ≥ 5 to < 14 years) or 21 (for subjects aged ≥ 2 to < 5 years) items and measures 7 domains: Physical Functioning, Emotional Functioning, School Functioning, Social Functioning, Psychosocial Summary, Physical Health, Total Score. Higher scores indicate better health status.
- **Patient Satisfaction Questionnaire** – This questionnaire is a non-validated measure that assesses the subject's (or via their caregiver) level of satisfaction with their treatment. For BAX 855 naïve subjects and BAX 855 naïve surgery subjects[xiv], at the end of study visit, the questionnaire also assesses the subject's preference between his previous treatment prior to the study and BAX 855. This questionnaire will be administered to all age groups.
- **Patient Activity Level** – Subjects will also be asked to estimate their activity levels. This will consist of a few questions asking subjects (or their caregiver) to rate their current level of activity. These data will be collected for all age groups.

xiv ie, subjects transitioning from the surgery study (Study 261204) into this continuation study that were naïve to BAX 855 prior to entry into the surgery study.

In addition, the following will be collected where applicable, for each occurrence:

- **Health Resource Use** – The subject (or their caregiver) will record the following events: (1) days missed from work/school (as appropriate) and days not able to perform normal activities outside of work/school due to hemophilia, (2) physician office visits, (3) hemophilia treatment site visits, (4) emergency room visits (reason and number), and (5) hospitalizations (reason, dates of hospitalization and associated length of stay). These data will be collected for all age groups.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation eCRF, including: completed, screen failure, AE (eg, death), discontinuation by subject (eg, lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (eg, pregnancy, progressive disease, non-compliance with IP/protocol violation(s)), study terminated by sponsor, or other (reason to be specified by the investigator, eg, technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded in the appropriate eCRF.

Every effort will be made to have discontinued subjects complete the study completion/termination visit. If the completion/termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the completion/termination visit. If a subject terminates participation in the study and does not return for the completion/termination visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.3 Schedule of Study Procedures and Assessments and Supplement 20.4 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take

place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.7 Procedures for Monitoring Subject Compliance

Subject compliance with the prescribed BAX 855 prophylaxis regimen will be monitored by review of subject diaries as described in Section 10.5.1. Other study procedures will be performed under the direct supervision of the investigator/a licensed healthcare professional at the study site, and thus, no other procedures for monitoring will be employed.

11. ASSESSMENT OF EFFICACY

11.1 Annualized Bleed Rate (ABR)

The primary measure of efficacy is the ABR. The ABR will be assessed based upon each individual bleeding episode, spontaneous or traumatic, recorded in the subject's diary, and/or recorded in the physician/nurse/clinic notes. A bleeding episode is defined as subjective (eg, pain consistent with a joint bleed) or objective evidence of bleeding which may or may not require treatment with FVIII. Bleeding episodes occurring at the same anatomical location (eg, right knee) with the same etiology (eg, spontaneous vs. injury) within 24 hours (± 2 hours) of onset of the first episode will be considered a single bleeding episode. Bleeding occurring at multiple locations related to the same injury (eg, knee and ankle bleeds following a fall) will be counted as a single bleeding episode.

11.2 Overall Hemostatic Efficacy Rating of BAX 855 for the Treatment of Bleeding Episodes

The subject or their caregiver will rate the severity (minor, moderate, or major) of the bleeding episode and will rate the overall treatment response at 24 (± 2) hours after the initiation of treatment using a 4-point efficacy rating scale (Table 4). Efficacy will not be assessed if any other FVIII concentrate is administered for the treatment of bleeding episodes. Since the efficacy rating is based to a large degree on cessation of pain, the investigator/subject shall, in particular in case of injury-related bleeding into one or more than one location, consider the injury-related symptoms when performing the efficacy rating 24 hours after initiating treatment and at resolution of bleed.

As per Table 4, multiple infusions of BAX 855 may be administered for the treatment of a bleeding episode. The overall response to all infusions combined is the rating that will be recorded.

Table 4 **Efficacy Rating Scale for Treatment of Bleeding Episodes at 24 ± 2 Hours from the Initiation of Treatment and at Resolution of Bleed**	
Excellent	Full relief of pain and cessation of objective signs of bleeding (eg, swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	Slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution.
None	No improvement or condition worsens.

Details pertaining to all treatments for each bleed, including response to treatment, will be recorded by study subjects/subjects' caregiver in subject diaries provided by the sponsor or sponsor's representative. At each study visit, the investigator will review together with the subject/subject's caregiver the response to treatment and evaluate the hemostatic efficacy rating. It may become necessary to re-discuss the rating with the subject/subject's caregiver to ensure the Rating Scale is fully understood:

- Any inconsistency between the efficacy rating and the number of infusions used to treat a bleeding episode, or a response to treatment rated as "none" must be immediately clarified.
- If 2 or more responses to treatment of unique bleeding episodes are rated "fair", the investigator may re-evaluate the dosing regimen and the time from bleeding onset to the start of treatment. If a bleeding episode requires only one infusion but response to treatment is rated "fair", the rating should be evaluated and the Rating Scale should be reviewed with the subject/subject's caregiver.
- If more than one infusion was given to treat a bleeding episode, and the treatment was rated "excellent", additional information should be provided about the severity of the bleeding episode (see Table 3) and/or whether additional infusions were given to maintain hemostasis. If infusions were given to maintain hemostasis after resolution of bleed, this should be recorded accordingly in the eCRF.

11.3 Number of BAX 855 Infusions Needed for the Treatment of Bleeding Episodes

The number of BAX 855 infusions to treat each bleeding episode is determined by the subject, the subject's caregiver, and/or investigator, and is based upon the subject's response to treatment. An infusion is defined as completion of administration of the calculated dose of BAX 855. If an infusion is interrupted, eg, due to vascular access issues, and must be re-started, it will be recorded as 1 infusion. If an infusion is terminated for any reason prior to completion of infusion and not restarted, it will be recorded as an infusion; reasons for interruption of the infusion will be recorded.

11.4 Time Intervals Between Bleeding Episodes

The time interval between bleeding episodes will be calculated based upon the date and time reported for each bleeding episode. The subject, the subject's caregiver, and/or investigator will determine when a bleeding episode has occurred (see Section 11.1 above).

11.5 Weight-Adjusted Consumption of BAX 855

Weight-adjusted consumption of BAX 855 will be determined based upon the amount of BAX 855 infused, as record in subject's diary and the subject's weight, as measured at the study site.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

An AE is defined as any untoward medical occurrence in a subject administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

A **serious** adverse event (SAE) is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.

- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (ie, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
  - Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V). Seroconversion to HBV is only considered an SAE in the absence of vaccination; seroconversion of HBsAb from negative to positive will not be considered an SAE (or an AE)
  - Development of a confirmed inhibitor to FVIII with an inhibitor level $\geq$ 0.6 BU, as measured by the Nijmegen assay modification of the Bethesda assay
  - Severe hypersensitivity/allergic reactions to BAX 855

Uncomplicated pregnancies, following maternal exposure to IP are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.

12.1.1.2 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.1.1.3 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (eg, IB, package insert). "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

For the purposes of this study, each unexpected AE experienced by a subject undergoing study-related procedures will be recorded on the AE eCRF.

12.1.1.4 Preexisting Diseases

For subjects transitioning into this continuation study from a prior BAX 855 study, any AEs that occurred during these other BAX 855 studies and which are still ongoing in this continuation study will be considered as "ongoing" and not as a preexisting disease.

AEs that were resolved in the previous BAX 855 studies will be documented as medical history for subjects who enter this continuation study. If a subject exited this continuation study to participate in the surgery study, upon return, any AEs that started and resolved during the surgery study will be documented as medical history.

Preexisting diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE eCRF.

12.1.2 Assessment of Adverse Events

Each AE from the first IP exposure until study completion/discontinuation will be described on the AE eCRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE eCRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first). If the severity rating for an ongoing AE changes before the event resolves, the original AE

report will be revised (ie, the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including overdosing, underdosing, abuse, and withdrawal, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Form and followed-up at 1 year post-delivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness; no additional reporting on eCRFs is necessary.

12.1.2.1 Severity

Subjects transitioning from a prior BAX 855 study who experienced an AE that has not resolved, will have any ongoing AEs and changes in severity of AEs documented as part of the safety data for the BAX 855 continuation study.

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, eg, assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not associated with the IP (ie, does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive rechallenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committee is notified of the urgent measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (ie, from the time of signed informed consent up to but not including the first IP exposure) will be described on the SAE Report. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

For the purposes of this study, each non-serious untoward medical occurrence experienced by a subject undergoing study-related procedure(s) before the first IP exposure will be recorded on the AE eCRF; these events will not be considered as AEs and will not be included in the analysis of AEs.

For the purposes of this study, each of the following non-serious events experienced after the first IP exposure will not be considered an AE, and thus, not included in the analysis of AEs:

- Hospital or study site visits for administration of BAX 855.

- Hospitalizations for routine bleeding episode management that could be managed in the study site or home-setting.
- Hospitalizations for planned medical or surgical procedures, eg, placement of a central venous line.
- Hospitalization or prolongation of hospitalization intended only for social reasons.
- Hospital admittance without inpatient hospitalization or emergency room visit/admittance in itself (although the event triggering the visit may be an SAE).
- Seroconversion after documented HAV/HBV vaccination prior to or during the study period.
- Bleeding episodes/hemophilia-related events:
  Bleeding episodes are part of the underlying disease and therefore are not considered AEs; they will be evaluated in the context of efficacy. If a bleeding episode was caused by an injury (eg, a fall), the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (eg, abrasion of skin; fractured tibia). However, the investigator may decide that a bleeding episode is an AE if the episode also would have occurred in a healthy individual under the same circumstances. Therefore, **any hemophilia-related event** (eg, hemarthrosis, bruising, hemorrhage) **will not be reported as an AE, but these events will be recorded on the bleeding episode eCRF**. However, hemophilia-related events meeting the criteria for seriousness (eg, a gastrointestinal hemorrhage requiring hospitalization) will be reported as SAEs and described on the SAER.

For subjects entering from other BAX 855 studies, the outcome of any ongoing AEs will be reported in this continuation study.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE.** NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, eg reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (eg, potential counterfeiting/tampering)

- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary; metabolic; infectious disease; and psychiatric.

All medications taken and non-drug therapies received from 30 days before enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies eCRFs.

Any prior use of any PEGylated medication (name of drug, indication, and dates of use), at any time in the past, will be recorded on the eCRF.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Supplement 20.3), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history eCRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE eCRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.4), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.7 Clinical Laboratory Parameters

All assessments will be performed at a central laboratory, according to the laboratory manual.

12.7.1 Hematology, Clinical Chemistry and Lipid Panel

Hematology, clinical chemistry and lipid assessments will be performed on EDTA-anticoagulated whole blood and serum, respectively.

The hematology panel will consist of complete blood count [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count), and leukocytes (ie, white blood cell count)] with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils, as a percentage of total white blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), CD4 counts (at screening only) and platelet counts.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, protein, albumin, alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, and glucose.

The lipid panel will consist of cholesterol, very low density lipoprotein (VLDL), low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides.

Details on the sampling of blood for assessment of hematology, clinical chemistry and lipid parameters are presented in Supplement 20.3 and Supplement 20.4.

12.7.2 Blood Type

For subjects who do not have documentation of their blood type in their medical record, blood ABO blood type will be determined.

12.7.3 Gene mutations and human leukocyte antigen (HLA) genotype

To test for FVIII gene mutations in BAX 855 naïve subjects, the cell pellets (buffy coat and erythrocytes) from the initial FVIII activity sample will be retained after collection of the plasma supernatant. Cell pellets will be labeled and stored at ≤ -70°C. FVIII gene mutation and HLA genotype testing will be performed at the central laboratory. The results will be provided to the sites. The investigator will be responsible for informing the subject of the test results. If results of FVIII gene mutation analysis and HLA genotype are already available at the study site, they will be provided to the sponsor and an additional analysis will be performed.

12.7.4 Factor VIII Activity, FVIII and VWF Antigen

FVIII activity will be measured using the one-stage clotting assay and the chromogenic assay. FVIII antigen will be measured using an enzyme-linked immunosorbent assay (ELISA). VWF antigen will only be measured pre-infusion for PK and IR determination

for FVIII activity as well as for FVIII activity trough level measurements[xv] using an ELISA.

12.7.4.1 Pharmacokinetic Evaluation for PK-Tailored Dosing

An abbreviated PK assessment will be performed in subjects who will receive a PK-tailored dosing and who have not undergone a PK assessment in a previous BAX 855 protocol or who are BAX 855 naïve. Blood samples for the PK evaluation will be collected at the following time points:

Subjects aged ≥ 12 years

Pre-infusion: Within 30 minutes prior to infusion

Infusion: 60 ± 5 IU/kg BAX 855[xvi]

Post-infusion: 15 minutes ± 5 minutes
3 hours ± 30 minutes
9 hours ± 30 minutes
32 hours ± 2 hours
56 hours ± 4 hours
96 hours ± 4 hours

Subjects aged < 12 years

Pre-infusion: Within 30 minutes prior to infusion

Infusion: 60 ± 5 IU/kg BAX 855[xvii]

Post-infusion: 15 minutes ± 5 minutes
9 hours ± 30 minutes
56 hours ± 4 hours

[xv] Note: Only in subjects receiving PK-tailored prophylaxis. In these subjects, VWF antigen measurement is optional for subjects aged < 12 years. Additionally, VWF antigen measurement is optional for subjects receiving a fixed dose prophylaxis.

xvi Preferably, only vials of the same lot with a nominal potency of 500 IU should be used for PK assessment in individual subjects. Alternatively, 1000 IU vials of the same lot could be used (see Section 8.7.2 for further details).

xvii Preferably, only vials of the same lot with a nominal potency of 500 IU should be used for PK assessment in individual subjects. Alternatively, 1000 IU vials of the same lot could be used (see Section 8.7.2 for further details).

Note: The PK assessment must be performed at least 84 to preferably 96 hours following the previous dose of BAX 855 or at least 72 hours following the previous dose of another FVIII concentrate and the subject must not be actively bleeding.

The PK infusion may be administered via a central line or a peripheral vein. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution. All PK samples will be collected through a peripheral vein. Blood samples drawn during the first 3 hours after BAX 855 administration will be drawn from a peripheral vein in an extremity distinct from the one that was used for product infusion. After that time, a vein in any appropriate extremity may be used.

Subjects who have a bleeding episode during the PK assessment period will not have subsequent PK blood samples taken. They will be treated for the bleeding episode, as appropriate (ie, for subjects that transitioned from a previous BAX 855 study, the bleed will be treated with BAX 855; for BAX 855 naïve subjects, the bleed will be treated with their current FVIII treatment). Subsequently, once recovered, subjects will be re-infused for PK assessment following a washout period of at least 84 to preferably 96 hours following the previous dose of BAX 855 or at least 72 hours following the previous dose of another FVIII concentrate. However, depending on the time point of the bleeding episode during the PK evaluation, an exemption may be granted by the sponsor.

12.7.4.2 Determination of FVIII Activity Trough Levels

FVIII activity trough levels will be measured in those subjects receiving a PK-tailored treatment regimen to ensure that FVIII trough levels of at least 3% are maintained. The blood sampling for FVIII activity, TGA parameters (optional for subjects aged < 12 years) and VWF antigen (optional for subjects aged < 12 years) should be performed immediately prior to the next regular prophylactic infusion, thus maintaining the treatment regimen-specific interval defined for each subject.

Details on the sampling of blood for determination of FVIII trough levels are presented in Supplement 20.3 and Supplement 20.4.

12.7.4.3 Determination of Incremental Recovery

Following a wash-out period of at least 84 to preferably 96 hours, FVIII activity trough levels will be measured within 30 minutes prior to the administration of 60 ± 5 IU/kg of BAX 855 as well as peak levels 30 ± 5 minutes after the infusion of BAX 855 for the determination of IR.

Details on the sampling of blood for determination of incremental recovery are presented in Supplement 20.3 and Supplement 20.4.

12.7.5 TGA Testing

The following thrombin generation assay (TGA) parameters will be assessed[xviii]: lag time, time to peak thrombin generation, peak thrombin generation, and endogenous thrombin potential [ETP]. These parameters will be determined using the calibrated, automated thrombin generation method.

Details on the sampling of blood for TGA testing are presented in Supplement 20.3 and Supplement 20.4.

12.7.6 Immunogenicity Assays

The primary study and safety assessment is the immunogenicity of BAX 855 which will be assessed by measurement of the following antibodies:

- Inhibitory antibodies to FVIII – measured by the Nijmegen modification of the Bethesda assay
- Binding antibodies to FVIII, BAX 855, and PEG. Both IgG and IgM antibodies will be measured using an ELISA assay.
- Anti-CHO antibodies

To avoid an impact of residual FVIII in plasma, subjects must undergo washout period of at least 84 to preferably 96 hours following the last BAX 855 infusion or at least 72 hours following the last infusion with another FVIII concentrate at the screening, follow-up and end of study visits, as well as prior to a potential unscheduled test. Additionally, the subject should be in a non-bleeding state.

A low titer (responder) inhibitor is defined as ≤ 5 BU but ≥ 0.6 BU. A high titer (responder) inhibitor is defined as > 5 BU by Nijmegen modification of the Bethesda assay. Inhibitors must be confirmed by 2 separate assessments within a 2 to 4 week period from the central laboratory.

Inhibitory antibodies to FVIII will be measured using the Nijmegen modification of the Bethesda inhibitor assay.

[xviii] Note: Measurement of TGA parameters is optional in subjects on fixed dose prophylactic treatment regimen and subjects aged < 12 years on PK-tailored prophylactic treatment regimen.

Binding antibodies (IgG and IgM) to FVIII and BAX 855, as well as to PEG, will be measured routinely using ELISA. Based on the variability of these tests, only samples with titers ≥ 1:80 can be confirmed and will be evaluated as positive. Furthermore, only increases of more than 2 titer steps between pre- and post-treatment samples will be considered positive for treatment-related antibody development. IgG subclass 1-4, IgA (using ELISA) and IgE antibodies (using ImmunoCaps, Phadia) may be assessed as clinically indicated.

The assay for antibodies to CHO protein will use CHO protein derived from cultures of untransfected cells. Testing for binding of anti-CHO protein antibodies will be performed on citrate-anti-coagulated plasma using an ELISA employing polyclonal anti-human IgG antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

Details on the sampling of blood for these assessments are presented in Supplement 20.3 and Supplement 20.4.

12.7.7 Viral Serology

Viral serology testing will include HIV-1 and HIV-2 antibody, HBsAb, HBsAg, HBcAb, and HCV Ab. HCV or HIV titer will be confirmed by PCR for all subjects reported as HCV or HIV positive. All assessments will be performed at the screening visit only. For BAX 855 naïve subjects, any positive test will be repeated using a new blood sample in case the positivity is not part of the medical history.

12.7.8 Assessment of Laboratory Values

12.7.8.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each laboratory value will be recorded on the eCRF. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes an new AE (see definition in Section 12.1, and record the sign, symptom, or medical diagnosis on the AE eCRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.4), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, ie because it is due to a preexisting disease, due to a lab error, or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

Any seroconversion result for HIV, HBV, or HCV shall be re-tested.

12.7.9 Biobanking

Depending on the subject's age and local regulations, backup samples will be taken (no backup samples will be taken for subjects aged < 6 years; only backup samples for inhibitory antibodies to FVIII and citrated plasma will be taken for subjects aged ≥ 6 and < 12 years) and stored appropriately for additional analysis, if necessary. These samples may be used for re-testing, tests required per regulatory guidelines, further evaluation of an AE, or follow-up of other test results.

Backup samples that remain after study testing is done may be stored and used for additional testing (eg, further evaluation of an abnormal test or an AE). Samples will be stored in a coded form for no more than 2 years after the final study report has been completed and subsequently will be destroyed.

12.8 Vital Signs

Vital signs will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (for subjects less than 18 years of age at the time of enrollment) (in or cm) and weight (lb or kg) will also be collected.

Vital signs will be measured at the screening visits, start of prophylaxis visit, follow-up visits, and end of study visit.

Blood pressure will be measured when subjects are in the supine position.

Vital sign values are to be recorded on the eCRF. For each abnormal vital sign value, the investigator will determine whether or not to report an AE (see definition in Section 12.1 and record the medical diagnosis (preferably), symptom, or sign on the AE eCRF). Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

13. STATISTICS

13.1 Sample Size and Power Calculations

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

13.2 Datasets and Analysis Cohorts

13.2.1 Safety Analysis Set

The safety analysis set will comprise all subjects treated with at least 1 BAX 855 infusion. All safety analyses will be performed on the safety analysis set.

13.2.2 Full Analysis Set

The full analysis set will be the same as the safety analysis set. All efficacy analyses will be performed on the full analysis set.

13.2.3 Per Protocol Analysis Set

The per protocol (PP) analysis set will comprise all subjects from the full analysis set who have no major deviations from the protocol affecting the study results. Major protocol deviations are defined in the Protocol Deviation Plan.

13.2.4 Analysis Cohorts

In addition to the overall subject group, subgroups of subjects on (1) fixed dose prophylactic treatment regimen and (2) PK-tailored prophylactic treatment regimen will be analyzed separately.

13.3 Handling of Missing, Unused, and Spurious Data

Missing data will not be imputed.

13.4 Methods of Analysis

13.4.1 Primary Outcome Measure

13.4.1.1 Primary Safety Outcome Measure

The number and proportion (Clopper-Pearson exact 95% CI) of subjects having been exposed to BAX 855 who develop inhibitory antibodies to FVIII (≥ 0.6 BU) will be provided.

13.4.1.2 Primary Efficacy Outcome Measure

The spontaneous ABR will be assumed to have a negative binomial distribution, and the mean ABR (95% CI) will be estimated using a general estimating equation (GEE) model framework (with a logarithmic link function which is the default for the negative binomial distribution) with treatment regimen as a fixed effect, subject effect as a random effect, age at baseline as a continuous covariate, and the logarithm of follow-up time (in years) as an offset.

13.4.2 Secondary Outcome Measures

13.4.2.1 Secondary Efficacy Outcome Measures

The total ABR (spontaneous and traumatic bleeding episodes) will be estimated and described similarly as the primary efficacy outcome measure.

The efficacy of BAX 855 in the treatment of bleeds will be summarized. It includes overall hemostatic efficacy rating at 24 (±2) hours after initiation of treatment and at resolution of bleed, number of BAX 855 infusions to control bleeding and total weight-adjusted dose per bleeding episode (excluding any infusions given to maintain hemostasis after the bleeding was controlled), and time interval between bleeding episodes.

Frequency tables will be prepared for the number of BAX 855 infusions required for the treatment of bleeding episodes. The median number of infusions (and nonparametric 95% CI) will be estimated.

Weight-adjusted consumption of BAX 855 for prophylaxis, treating bleeding episodes (excluding any infusions given to maintain hemostasis after the bleeding is controlled) and in total per subject will be summarized separately as average number of BAX 855 infusions and average weight-adjusted consumption of BAX 855 per month.

The average time interval between 2 consecutive bleeding episodes will be computed for each subject as the duration of the observation period divided by the number of bleeding episodes in the observation period. The median (95% CI) of those average time intervals between 2 bleeding episodes will be estimated.

13.4.3 Pharmacokinetics

For subjects undergoing a PK assessment in this study, the following PK parameters for FVIII will be reported using descriptive statistics: AUC0-∞, $T_{1/2}$, MRT, CL, IR, Cmax and Vss.

For subjects undergoing a PK assessment in this study, an exploratory analysis of correlation of baseline VWF antigen to BAX 855 PK will be performed as well as the possible influence of any anti-PEG antibodies (preexisting or detected during study participation) on the PK of BAX 855, if applicable.

IR will be summarized by visit and displayed graphically over time for each subject. Also the change from the baseline will be described using summary statistics.

13.4.4 Secondary Safety Outcome Measures

Frequency counts and percentages will be calculated for SAEs, occurrence of inhibitory antibodies to FVIII, occurrence of binding antibodies to FVIII, BAX 855 and PEG, occurrence of anti-CHO antibodies, and occurrence of hypersensitivity reactions.

AEs that occurred during or after treatment will be presented in summary tables. AEs will be cross-tabulated for relatedness, seriousness, and severity. AEs will be categorized according to the MedDRA dictionary and summarized by system organ class and preferred term.

Vital signs and clinical laboratory parameters will be characterized descriptively. Shift tables will be prepared for laboratory parameters. Clinically significant abnormal values in routine laboratory parameters (hematology, clinical chemistry, lipids) and vital signs will be summarized.

13.4.5 Patient Reported Outcomes

13.4.5.1 Haemo-SYM

Bleed and pain severity will be measured using the Haemo-SYM questionnaire with higher scores on the Haemo-SYM indicating more severe symptoms. Changes from baseline in the Haemo-SYM scores will be tested for statistical significance using a Wilcoxon test for paired samples. Number and proportion of subjects with an improvement in the Haemo-SYM pain subscale will be tabulated.

13.4.5.2 SF-36

HRQoL in subjects aged ≥ 14 years will be measured using the SF-36 questionnaire with lower scores on SF-36 indicating worse HRQoL. Changes from baseline in the SF-36 scores will be tested for statistical significance using a Wilcoxon test for paired samples. Number and proportion of subjects with an improvement in the SF-36 will be tabulated.

13.4.5.3 PedsQL

HRQoL in subjects aged < 14 years will be measured using the PedsQL with lower scores on the PedsQL indicating worse HRQoL. Changes from baseline in the PedsQL scores will be tested for statistical significance using a Wilcoxon test for paired samples. Number and proportion of subjects with an improvement in the PedsQL will be tabulated.

13.4.6 Exploratory Outcome Measures

Patient satisfaction with treatment, patient activity level and health resource use data will be descriptively summarized and listed.

The potential influence of TGA parameters and FVIII trough levels on ABR in the three months after TGA/FVIII trough level measurement will be explored by scatterplots for all subjects who have TGA tested.

13.5 Planned Interim Analysis of the Study

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

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

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Study Agreement. If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the Clinical Study Agreement.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable regulatory requirements as described in the Clinical Study Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Clinical Study Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

15.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxalta) will also ensure the responsible ethics committee is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.6 Laboratory and Reader Standardization

Not applicable; a central laboratory/reader will be used for all clinical assessments.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the Clinical Study Agreement.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the Clinical Study Agreement.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable regulatory requirements and ICH GCP. An assent form may be provided and should be signed by patients less than 18 years of age. Before use, the informed consent/assent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The informed consent/assent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable regulatory requirements. Patients and/or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent/assent form, patients and/or their legally authorized representative(s) agree that they will complete all

evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent/assent will be updated, if necessary. This new information and/or revised informed consent/assent form, that have been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects and/or subjects' legally authorized representative who consented to participate in the study (see Section 16.3).

16.4 Data Monitoring Committee

A Data Monitoring Committee (DMC) will not be used for this study as the expected related AEs in this study are anticipated to be similar to that of the licensed product ADVATE (of which the core protein is identical to that of BAX 855; see Section 6.5 for more details on anticipated risks and benefits of BAX 855). Additionally, the safety is not expected to differ from the safety observed in the BAX 855 pivotal and pediatric study (Studies 261201 and 261202, respectively).

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the Clinical Study Agreement.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.8), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, eCRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the eCRFs. CRFs will be provided in electronic form.

If electronic format eCRFs are provided by the sponsor, only authorized study site personnel will record or change data on the eCRFs. If data is not entered on the eCRFs during the study visit, the data will be recorded on paper, and this documentation will be considered source documentation. Changes to a eCRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of eCRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (eg, ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Clinical Study Agreement.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Study Agreement.

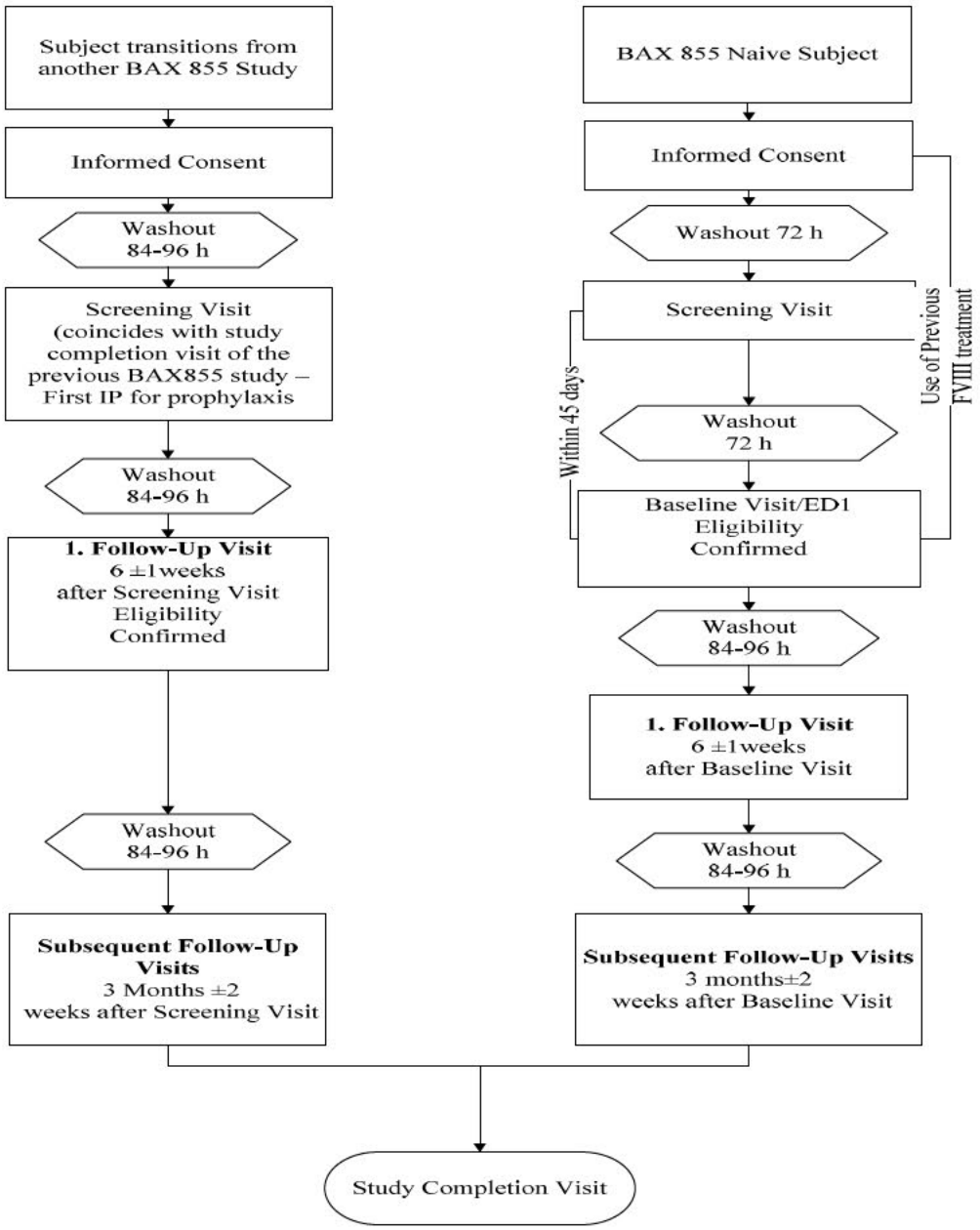
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

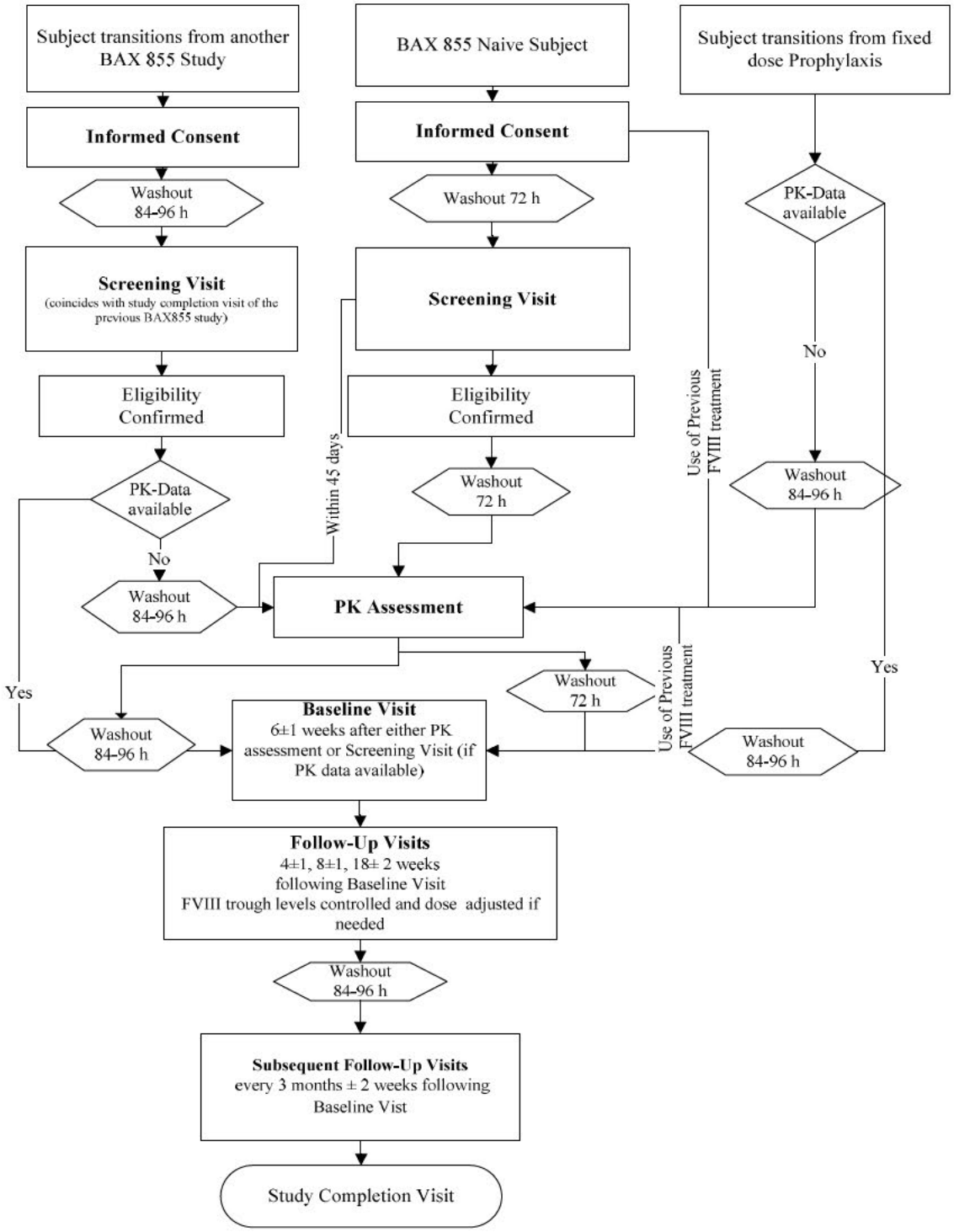
20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 1
Study Design for Baxalta Clinical Study 261302
Subjects on Fixed Dose Prophylactic Treatment Regimen



Subjects on PK-Tailored Prophylactic Treatment Regimen



20.2 Flow Diagram of Study Procedures

20.2.1 Subjects on Fixed Dose Prophylactic Treatment Regimen

20.2.1.1 Screening Visit

The screening procedures differ according to whether the subject is **transitioning from a previous BAX 855 study** (see Section 20.2.1.1.1) or is **BAX 855 naïve** (see Section 20.2.1.1.2). From the visit at 6 ± 1 weeks onwards, procedures for these 2 sets of subjects are identical.

20.2.1.1.1 Subjects transitioning from other BAX 855 studies

The screening visit coincides with the end of study visit of the previous BAX 855 study.

Informed consent must be obtained at enrollment at the latest (prior to any study-specific procedure); to give the patient sufficient time to review the ICF, this document should preferably be provided prior to the end of study visit of the previous study.

At least 84 to preferably 96 hours must have elapsed since the previous BAX 855 administration and the subject must not be actively bleeding.

The relevant data obtained at the end of study visit of the previous BAX 855 study will be transcribed to the screening visit eCRF of this continuation study, and where possible, duplication of blood draws or evaluations will be avoided.

<u>The following procedures will be performed:</u>

Pre-infusion:

- Ensure informed consent has been obtained
- Assess performance score (Karnofsky [≥ 16 years] or Lansky [< 16 years])
- Laboratory assessments:
    - Viral serology:
        - HIV: HIV-1 and HIV-2 Ab (PCR to be performed if positive)
        - HBV: HBsAg, HBsAb, HBcAb
        - HCV: HCVAb (PCR to be performed if positive)
    - CD4 count, if subject is HIV positive
- Pregnancy test if female of childbearing potential
- Assessment of inclusion/exclusion criteria
- PROs:
    - Bleed and pain severity using Haemo-SYM (≥ 18 years), HRQoL using SF-36 (≥ 14 years), HRQoL using PedsQL (< 14 years), patient satisfaction with treatment using the Satisfaction Questionnaire (all ages), and Patient Activity Level (all ages)
- Provide a subject e-diary and give instructions on use.

The following data will be obtained/transcribed from the end of study visit of the previous BAX 855 study:

- Medical History
- Medication history
- Concomitant medications
- Non-drug therapies
- Physical examination
- Vital signs
- Adverse events

- Laboratory data[xix]:
    - FVIII activity (activated partial thromboplastin-based 1-stage clotting assay and chromogenic assay) and FVIII antigen
    - Immunogenicity tests: Inhibitory antibodies to FVIII (Nijmegen assay), binding antibodies (IgG and IgM) to FVIII, BAX 855, and PEG, anti-CHO antibodies
    - Hematology, clinical chemistry, and lipid panel

BAX 855 Infusion:

- Administration of first fixed dose prophylactic infusion of BAX 855.

  OR
- If IR is to be assessed (BAX 855 pivotal: optional; BAX 855 surgery: not applicable): Administration of 60 ± 5 IU/kg of BAX 855

Post-infusion:

At 30 ± 15 min post-infusion:

- FVIII : FVIII activity (1-stage clotting assay and chromogenic assay) and FVIII antigen
- Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure)

Other procedures:

- Dispense IP:
    - A sufficient quantity of IP will be dispensed to cover the period until the next scheduled visit in 6 ± 1 weeks.

20.2.1.1.2 BAX 855 naïve subjects

At least 72 hours must have elapsed since the previous FVIII administration and the subject must not be actively bleeding.

Evaluations must be completed within 45 days prior to the first infusion of BAX 855 on ED1 (baseline).

<u>The following procedures will be performed:</u>

- Ensure informed consent has been obtained
- Medical history
- Hemophilia history, including:
    - Confirmation of diagnosis and severity
    - Family history of hemophilia
    - Documentation of mutation, if known
    - The presence of any target joints will be documented. A target joint is defined as any single joint (ankles, knees, hips, or elbows) with ≥ 3 spontaneous bleeding episodes in any consecutive 6 month period.
    - Documentation of all FVIII replacement therapies used within the last year, including:
        - FVIII regimen (prophylaxis or on-demand)
        - Product name (or IP name and manufacturer, if applicable)
        - Dose (for prophylaxis, if applicable, and for treatment of bleeding episodes)
        - Frequency of administration (for prophylaxis)

[xix] Note: for subjects transitioning from the surgery study (Study 261204), FVIII activity and FVIII antigen and lipid panel should also be performed.

- Estimate of average number of infusions for each bleeding episode and usual response
- Medications received in last 30 days, and any prior history of use of any PEGylated medication (eg, PEG-interferon) at any time in the past, including treatment indication, date of last administration, and duration of treatment(s), if known
- Non-drug therapies
- Physical examination, including height (for subjects aged < 18 years at enrollment) and weight
- Assess performance score (Karnofsky [≥ 16 years] or Lansky [< 16 years])
- Vital signs (body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), and supine systolic and diastolic blood pressure (mmHg)).
- Laboratory assessments:
  - Screening tests:
    - CD4 count, if subject is HIV positive
    - Viral serology (if any positive, test to be confirmed with a second sample):
      - HIV: HIV-1 and HIV-2 Ab (PCR to be performed if positive)
      - HBV: HBsAg, HBsAb, HBcAb
      - HCV: HCVAb (PCR to be performed if positive)
    - Genetics (FVIII gene mutation analysis) and HLA-genotype, if applicable
    - Blood type (A, B, AB or O) if historical data not available (local laboratory)
  - FVIII assays:
    - FVIII activity (activated partial thromboplastin-based 1-stage clotting assay and chromogenic assay)
    - FVIII antigen
  - Immunogenicity tests:
    - Inhibitory antibodies to FVIII (Nijmegen assay)
    - Binding antibodies (IgG and IgM) to FVIII, BAX 855, and PEG
    - Anti-CHO antibodies
  - Hematology, clinical chemistry, and lipid panel
- Pregnancy test if female of childbearing potential
- Assessment of inclusion/exclusion criteria
- Provide a subject e-diary and give instructions on use

20.2.1.2 ED1 (Baseline):

Only Applicable to BAX 855 Naïve Subjects

At least 72 hours must have elapsed since the previous administration of any FVIII concentrate, and the subject must not be actively bleeding.

<u>The following procedures will be performed:</u>

Pre-infusion:

- Confirmation of eligibility
- Physical examination, including height (for subjects aged < 18 years at enrollment) and body weight
- Review and discuss subject e-diary, including:
  - Review bleeding episodes and their treatment
  - Adverse events
  - Concomitant medications and non-drug therapies

- Laboratory assessments within 30 minutes of start of infusion:
    - FVIII activity and antigen
    - Immunogenicity tests
    - VWF antigen (optional)
    - TGA parameters (optional)
- PROs:
    - Bleed and pain severity using Haemo-SYM (≥ 18 years), HRQoL using SF-36 (≥ 14 years), HRQoL using PedsQL (< 14 years), patient satisfaction with treatment using the Satisfaction Questionnaire (all ages), and Patient Activity Level (all ages)
- Vital signs (within 15 minutes of start of infusion)

Determination of IR:

- Infusion of 60 ± 5 IU/kg BAX 855

Post-infusion:

At 30 ± 15 min post-infusion:

- FVIII activity and antigen
- TGA parameters (optional)
- Vital signs

Other procedures:

- Dispense IP:
    - A sufficient quantity of IP will be dispensed to cover the period until the next scheduled visit in 6 ± 1 weeks.

20.2.1.3 Follow-up Visits

- **At 6 (± 1) weeks from screening (transitioning subjects) or baseline (BAX 855 naïve subjects)**
- **Subsequently: Every 3 months (± 2 weeks) starting from screening (transitioning subjects) or baseline (BAX 855 naïve subjects)**

From this timepoint, procedures for subjects on the fixed dose prophylactic regimen are identical, apart from confirmation of eligibility for transitioning subjects at the 6 ± 1 weeks visit (which was done at ED1 for BAX 855 naïve subjects).

At least 84 to preferably 96 hours must have elapsed since the previous BAX 855 administration and the subject must not be actively bleeding.

<u>The following assessments will be performed:</u>

Pre-infusion:

- Confirmation of eligibility for transitioning subjects (at the 6 ± 1 weeks visit)
- Physical examination, including height (for subjects aged < 18 years at enrollment) and body weight
- Review and discuss subject e-diary, including:
    - Review bleeding episodes and their treatment
    - Adverse events
    - Concomitant medications and non-drug therapies
- Laboratory assessments within 30 minutes of start of infusion
    - FVIII activity and antigen

- TGA parameters (optional)
- VWF antigen (optional)
- Immunogenicity tests
- Hematology, clinical chemistry and lipid panel

- Vital signs (within 15 minutes of IP infusion)

Determination of IR

- Infusion of 60 ± 5 IU/kg BAX 855

Post-infusion:
At 30 ± 15 min post-infusion:

- FVIII activity and antigen
- TGA parameters (optional)
- Vital signs

Other procedures:

- Dispense IP:
  - A sufficient quantity of IP will be dispensed to cover the period until the next scheduled visit.

Intermittent procedures, every 6 months:

- Every 6 months PROs will be assessed:
  - Bleed and pain severity using Haemo-SYM (≥ 18 years), HRQoL using SF-36 (≥ 14 years), HRQoL using PedsQL (< 14 years), patient satisfaction with treatment using the Satisfaction Questionnaire (all ages), and Patient Activity Level (all ages).
- In subjects who are HIV positive, CD4 counts should be tested every 6 months.

20.2.1.4 End of Study Visit

The procedures listed here should also be performed if a subject withdraws or discontinues from the study. At least 84 to preferably 96 hours must have elapsed since the previous BAX 855 administration and the subject must not be actively bleeding.

<u>The following assessments will be performed:</u>
Pre-infusion:

- Physical examination, including height (for subjects aged < 18 years at enrollment) and body weight
- Pregnancy test if female of childbearing potential
- Collection of subject e-diary and review of entries and discussion with subject
  - Review bleeding episodes and their treatment
  - Adverse events
  - Concomitant medications and non-drug therapies
- PROs:
  - Bleed and pain severity using Haemo-SYM (≥ 18 years), HRQoL using SF-36 (≥ 14 years), HRQoL using PedsQL (< 14 years), patient satisfaction with treatment using the Satisfaction Questionnaire (all ages), and Patient Activity Level (all ages)
- Laboratory assessments within 30 minutes of start of infusion:
  - FVIII activity and antigen
  - TGA parameters (optional)

- VWF antigen(optional)
- Immunogenicity tests
- Hematology, clinical chemistry and lipid panel

- Vital signs (within 15 minutes of IP infusion)

Determination of IR

- Infusion of 60 ± 5 IU/kg BAX 855

Post-infusion:

At 30 ± 15 min post-infusion:

- FVIII activity and antigen
- TGA parameters (optional)
- Vital signs

20.2.2 Subjects on PK-Tailored Prophylactic Treatment Regimen

20.2.2.1 Screening Visit

Subjects who decide to **switch** to a PK-tailored treatment regimen at any time during the continuation study will start with the procedures from the PK assessment visit (if one is needed), but the screening visit is not applicable.

The screening procedures differ according to whether the subject is **transitioning from a previous BAX 855 study** (see Section 20.2.1.1.1) or is **BAX 855 naïve** (see Section 20.2.1.1.2).

20.2.2.1.1 Subjects transitioning from other BAX 855 studies

The screening visit coincides with the end of study visit of the previous BAX 855 study.

Informed consent must be obtained at enrollment at the latest (prior to any study-specific procedure); to give the patient sufficient time to review the ICF, this document should preferably be provided prior to the end of study visit of the previous study.

At least 84 to preferably 96 hours must have elapsed since the previous BAX 855 administration and the subject must not be actively bleeding.

The relevant data obtained at the end of study visit of the previous study will be transcribed to the screening visit eCRF of this continuation study, and where possible, duplication of blood draws or evaluations will be avoided.

<u>The following procedures will be performed:</u>

- Ensure informed consent has been obtained
- Assess performance score (Karnofsky [≥ 16 years] or Lansky [< 16 years])
- Laboratory assessments:
    - Viral serology:
        - HIV: HIV-1 and HIV-2 Ab (PCR to be performed if positive)
        - HBV: HBsAg, HBsAb, HBcAb
        - HCV: HCVAb (PCR to be performed if positive)
    - CD4 count, if subject is HIV positive
- Pregnancy test if female of childbearing potential
- Assessment of inclusion/exclusion criteria
- Provide a subject e-diary and give instructions on use.

The following data will be obtained/transcribed from the end of study visit of the previous BAX 855 study:

- Medical History
- Medication history
- Concomitant medications
- Non-drug therapies
- Physical examination
- Vital signs
- Adverse events
- Laboratory data[xx]:

[xx] Note: For subjects transitioning from the surgery study (Study 261204), FVIII activity and FVIII antigen and lipid panel should also be performed.

- FVIII assays: FVIII activity (activated partial thromboplastin-based 1-stage clotting assay and chromogenic assay) and FVIII antigen (pre- and post-infusion values, if IR assessed in previous study's end of study visit)
- Immunogenicity tests: Inhibitory antibodies to FVIII (Nijmegen assay), binding antibodies (IgG and IgM) to FVIII, BAX 855, and PEG, anti-CHO antibodies
- Hematology, clinical chemistry, and lipid panel

BAX855 Infusion:

- Administration of first prophylactic infusion of BAX 855 using a fixed dose prophylactic treatment regimen as used in the previous study.

OR

- If IR is to be assessed (BAX855 pivotal: optional; BAX855 surgery: not applicable):Administration of 60± 5 IU/kg of BAX855

  At 30 ± 15 min post-infusion:

  - FVIII: FVIII activity (1-stage clotting assay and chromogenic assay) and FVIII antigen
  - Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure)

Transitioning subjects who **have undergone a PK assessment** in a previous BAX 855 study do not need to undergo a PK assessment in this study, but can start their PK-tailored prophylactic treatment at the next visit (Baseline visit) at 6 ± 1 weeks after the screening visit. A sufficient quantity of IP will be dispensed to continue with their previous prophylactic BAX 855 treatment regimen until the Baseline visit. Subjects who received on-demand treatment in the pivotal study (Study 261201) will first receive a fixed dose prophylactic treatment regimen (as outlined in section 8.7.3.1) until their dose and frequency is determined and the first PK-tailored dose administered.

→ See Section "Baseline visit / Start of prophylaxis" (see Section 20.2.2.3) for further procedures

Those who **have not undergone a PK assessment** in a previous BAX 855 study must attend a PK assessment visit. A sufficient quantity of IP will be dispensed to continue with their previous BAX 855 treatment regimen until the PK assessment within 45 days from screening.

→ See Section "PK assessment for BAX 855 naïve subjects and transitioning subjects with no prior PK assessment" (see Section 20.2.2.2) for further procedures

20.2.2.1.2 BAX 855 naïve subjects

At least 72 hours must have elapsed since the previous FVIII administration and the subject must not be actively bleeding.

Evaluations must be completed within 45 days prior to the PK assessment.

The following procedures will be performed:

- Ensure informed consent has been obtained.
- Medical history
- Hemophilia history, including:
    - Confirmation of diagnosis and severity
    - Family history of hemophilia
    - Documentation of mutation, if known
    - The presence of any target joints will be documented. A target joint is defined as any single joint (ankles, knees, hips, or elbows) with ≥ 3 spontaneous bleeding episodes in any consecutive 6 month period.
    - Documentation of all FVIII replacement therapies used within the last year, including:
        - FVIII regimen (prophylaxis or on-demand)
        - Product name (or IP name and manufacturer, if applicable)
        - Dose (for prophylaxis, if applicable, and for treatment of bleeding episodes)
        - Frequency of administration (for prophylaxis)
        - Estimate of average number of infusions for each bleeding episode and usual response
- Medications received in last 30 days, and any prior history of use of any PEGylated medication (eg, PEG-interferon) at any time in the past, including treatment indication, date of last administration, and duration of treatment(s), if known
- Non-drug therapies
- Physical examination, including height (for subjects aged < 18 years at enrollment) and weight
- Assess performance score (Karnofsky [≥ 16 years] or Lansky [< 16 years])
- Vital signs (body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), and supine systolic and diastolic blood pressure (mmHg)).
- Laboratory assessments:
    - Screening tests:
        - CD4 count, if subject is HIV positive
        - Viral serology (if any positive, test to be confirmed with a second sample) :
            - HIV: HIV-1 and HIV-2 Ab
            - HBV: HBsAg, HBsAb, HBcAb
            - HCV: HCVAb (PCR to be performed if positive)
        - Genetics (FVIII gene mutation analysis) and HLA-genotype
        - Blood type (A, B, AB or O) if historical data not available (local laboratory)
    - FVIII assays:
        - FVIII activity (activated partial thromboplastin-based 1-stage clotting assay and chromogenic assay)
        - FVIII antigen

- Immunogenicity tests:
  - Inhibitory antibodies to FVIII (Nijmegen assay)
  - Binding antibodies (IgG and IgM) to FVIII, BAX 855, and PEG
  - Anti-CHO antibodies
- Hematology, clinical chemistry, and lipid panel
- Pregnancy test if female of childbearing potential
- Assessment of inclusion/exclusion criteria
- Provide a subject e-diary and give instructions on use

20.2.2.2 PK Assessment

For BAX 855 naïve subjects and transitioning subjects with no prior PK assessment

Blood sampling after infusion of BAX 855 for PK assessments will be performed over a 4-day period for subjects aged ≥ 12 years or a 2.5 day period for subjects aged < 12 years. A minimum wash-out period of 84 to preferably 96 hours prior to the PK infusion is required for subjects transitioning from another BAX 855 study and 72 hours prior to PK infusion for BAX 855 naïve subjects on treatment with any other FVIII concentrate, and the subject must not be actively bleeding.

The following assessments will be performed:

Pre-infusion

- Confirmation of eligibility
- Physical examination, including height (for subjects aged < 18 years at enrollment) and body weight
- Review and discuss subject e-diary, including:
  - Review bleeding episodes and their treatment
  - Adverse events
  - Concomitant medications and non-drug therapies
- Laboratory assessments within 30 minutes of start of infusion:
  - FVIII activity and antigen
  - Immunogenicity tests (BAX855 naïve subjects only)
  - TGA parameters and VWF antigen (optional in subjects aged < 12 years)
- Vital signs (within 15 minutes of start of infusion)

Infusion for PK assessment:

- Infusion of 60 ± 5 IU/kg BAX 855

Post-infusion:

- Laboratory assessments in subjects aged ≥ 12 years:
  - FVIII activity, FVIII antigen and TGA parameters at the following post-infusion time points: 15 min ± 5 min, 3 h ± 30 min, 9 h ± 30 min, 32 h ± 2 h, 56 h ± 4 h, and 96 h ± 4 h
- Laboratory assessments in subjects aged < 12 years:
  - FVIII activity and antigen at the following post-infusion time points: 15 min ± 5 min, 9 h ± 30 min, 56 h ± 4 h
  - Optional TGA parameters at the same timepoints
- Vital signs at 30 min ± 5 min post-infusion

Other procedures:

- Dispense IP to transitioning subjects:
    - A sufficient quantity of IP will be dispensed to cover the period until the next scheduled visit in 6 ± 1 weeks.

20.2.2.3 Baseline Visit / Start of Prophylaxis

This visit takes place 6 ± 1 weeks following the PK assessment, or following screening if a PK was already available in case of transitioning subjects. This visit will then coincide with confirmation of eligibility. It is the baseline time point for all subsequent visits.

At least 84 to preferably 96 hours must have elapsed since the previous BAX 855 administration and at least 72 hours since the previous administration of any other FVIII concentrate in case of BAX855 naïve subjects, and the subject must not be actively bleeding.

The following procedures will be performed:

Pre-infusion:

- Confirmation of eligibility for transitioning subjects with previous PK data
- Physical examination, including height (for subjects aged < 18 years at enrollment) and body weight
- Review and discuss subject e-diary, including:
    - Review bleeding episodes and their treatment (not applicable for BAX855 naïve subjects)
    - Adverse events
    - Concomitant medications and non-drug therapies
- Laboratory assessments within 30 minutes of start of infusion:
    - FVIII activity and antigen
    - TGA parameters and VWF antigen (optional in subjects aged <12 years)
    - Immunogenicity tests
    - Hematology, clinical chemistry, and lipid panel
- PROs:
    - Bleed and pain severity using Haemo-SYM (≥ 18 years), HRQoL using SF-36 (≥ 14 years), HRQoL using PedsQL (< 14 years), patient satisfaction with treatment using the Satisfaction Questionnaire (all ages), and Patient Activity Level (all ages)
- Vital signs (within 15 minutes of start of infusion)

Determination of IR:

- Infusion of 60 ± 5 IU/kg BAX 855

Post-infusion:

At 30 ± 15 min post-infusion:

- FVIII activity and antigen
- TGA parameters (optional in subjects aged < 12 years)
- Vital signs

Other procedures:

- Dispense IP:
    - A sufficient quantity of IP will be dispensed to cover the period until the next scheduled visit in 4 ± 1 week.

20.2.2.4 Follow-up Visits: At 4 (± 1) Weeks, 8 (± 1) Weeks, 18 (± 2) Weeks from Baseline Visit

No wash-out period is required for this visit and the patient should not be in a bleeding state.

The visit should be performed immediately prior to the next regular prophylactic infusion in order to determine adequate FVIII trough levels.

The following assessments will be performed:

Pre-infusion:

- Physical examination, including height (for subjects aged < 18 years at enrollment) and body weight
- Review and discuss subject e-diary, including:
  - Review bleeding episodes and their treatment
  - Adverse events
  - Concomitant medications and non-drug therapies
- Laboratory assessments within 30 minutes of start of infusion:
  - FVIII activity and antigen
  - TGA parameters and VWF antigen (optional in subjects aged < 12 years)
- Vital signs (within 15 minutes of IP infusion)

Infusion of the PK-tailored prophylactic dose of BAX 855

Other procedures:

- Dispense IP:
  - A sufficient quantity of IP will be dispensed to cover the period until the next scheduled visit
- Upon availability of the FVIII trough levels dose adjustments, if applicable

20.2.2.5 Follow-up Visits: Every 3 Months (± 2 Weeks) Starting from Baseline Visit

A washout period of at least 84 h to preferably 96 hours must have elapsed since the previous BAX 855 administration and the subject must not be actively bleeding.

The following assessments will be performed:

Pre-infusion:

- Physical examination, including height (for subjects aged < 18 years at enrollment) and body weight
- Review and discuss subject e-diary, including:
  - Review bleeding episodes and their treatment
  - Adverse events
  - Concomitant medications and non-drug therapies
- Laboratory assessments within 30 minutes of start of infusion:
  - FVIII activity and antigen
  - TGA parameters and VWF antigen (optional in subjects aged < 12 years)
  - Immunogenicity tests
  - Hematology, clinical chemistry and lipid panel
- Vital signs (within 15 minutes of IP infusion)

Determination of IR:

- Infusion of 60 ± 5 IU/kg BAX 855

Post-infusion

At 30 ± 15 min post-infusion:

- FVIII activity and antigen
- TGA parameters (optional in subjects aged < 12 years)
- Vital signs

Other procedures:

- Dispense IP:
    - A sufficient quantity of IP will be dispensed to cover the period until the next scheduled visit (ie, for 5 or 8 weeks or 3.5 months, depending on the visit).
- Dose adjustments as needed.

Intermittent procedures, every 6 months:

- Every 6 months PROs will be assessed:
    - Bleed and pain severity using Haemo-SYM (≥ 18 years), HRQoL using SF-36 (≥ 14 years), HRQoL using PedsQL (< 14 years), patient satisfaction with treatment using the Satisfaction Questionnaire (all ages), and Patient Activity Level (all ages).
- In subjects who are HIV positive, CD4 counts should be tested every 6 months.

20.2.2.6 End of Study Visit

The procedures listed here should also be performed if a subject withdraws or discontinues from the study. At least 84 to preferably 96 hours must have elapsed since the previous BAX 855 administration and the subject must not be actively bleeding.

<u>The following assessments will be performed:</u>

Pre-infusion:

- Physical examination, including height (for subjects aged < 18 years at enrollment) and body weight
- Collection of subject e-diary and review of entries and discussion with subject
    - Review bleeding episodes and their treatment
    - Adverse events
    - Concomitant medications and non-drug therapies
- PROs:
    - Bleed and pain severity using Haemo-SYM (≥ 18 years), HRQoL using SF-36 (≥ 14 years), HRQoL using PedsQL (< 14 years), patient satisfaction with treatment using the Satisfaction Questionnaire (all ages), and Patient Activity Level (all ages)
- Laboratory assessments within 30 minutes of start of infusion:
    - FVIII activity and antigen assays
    - TGA parameters and VWF antigen (optional in subjects aged < 12 years)
    - Immunogenicity tests
    - Hematology, clinical chemistry and lipid panel
- Vital signs (within 15 minutes of IP infusion)

Determination of IR:

- Infusion of 60 ± 5 IU/kg BAX 855

Post-infusion:
At 30 ± 15 min post-infusion:

- FVIII activity and antigen
- TGA parameters (optional in subjects aged < 12 years)
- Vital signs

20.3 Schedule of Study Procedures and Assessments

20.3.1 Subjects Transitioning from Other BAX 855 Studies on Fixed Dose Prophylactic Treatment Regimen

Procedures/Assessments	Screening Visit[a]	Follow-Up Visits		End of Study Visit[b]
		6 ± 1 Weeks Following Screening	Every 3 Months ± 2 Weeks Following Screening	
Informed consent[c]	X			
Eligibility criteria	X			
Confirmation of eligibility		X		
Medical history	*			
Medication history	*			
Concomitant medications[d]	*	X	X	X
Non-drug therapies[d]	*	X	X	X
Physical exam	*	X	X	X
Adverse events[d]	*	X	X	X
Laboratories[e]	*	X	X	X
Vital signs[f]	*	X	X	X
Bleeding episodes and their treatment[d]	*	X	X	X
Pregnancy test[g]	X			X
PROs[h]	X		X[i]	X
Patient e-diary[j]	X	X	X	X
IR determination[k]	X	X	X	X
Dispense IP	X[k]	X	X	

[a] The screening visit coincides with the end of study visit of the previous BAX 855 study. The procedures/assessments marked with an asterisk (*) will be transcribed from the end of study visit of the previous BAX 855 study. The following assessments are not part of the end of study assessments of the previous BAX 855 study and must be performed at screening to ensure eligibility: Performance score (Karnofsky or Lansky), viral serology (see Section 20.4.1), and pregnancy test if female of childbearing potential. Additionally, for subjects transitioning from the surgery study (Study 261204), FVIII assays and lipid panel (see Section 20.4.1) should also be performed.

[b] Including cases of withdrawal or discontinuation.

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[c] Occurs at enrollment at latest (prior to any study-specific procedure); to give the patient sufficient time to review the ICF, this document should preferably be provided prior to the end of study visit of the previous study.

[d] Indicates that concomitant medications, non-drug therapies, adverse events, and bleeding episodes and their treatment will be continuously reviewed and specifically assessed at these times by the study sites and discussed with the subject.

[e] For laboratory assessments, see Section 20.4.1.

[f] Vital signs to include body temperature (ºC), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg).

[g] A hCG urine pregnancy test will be done on all females of childbearing potential at the screening and end of study visit.

[h] PROs to include the following depending on patient age: bleed and pain severity using Haemo-SYM (≥18 years), HRQoL using SF-36 (≥ 14 years), HRQoL using PedsQL (< 14 years), patient satisfaction with treatment using the Satisfaction Questionnaire (all ages), and Patient Activity Level (all ages). PROs will be measured at start of prophylaxis treatment, every 6 months and at end of study.

[i] In addition to the screening and end of study visit, PROs will be assessed every 6 months following screening.

[j] E-diaries will be given out at screening and will be used to document bleeds, treatment administered and response to BAX 855, untoward events, concomitant medications and health resource use data. E-diaries are reviewed and discussed with the subject at each study visit.

[k] The first IP treatment at screening serves for the determination of the baseline IR and the end of study IR of the previous study, if applicable.

20.3.2 BAX 855 Naïve Subjects on Fixed Dose Prophylactic Treatment Regimen

Procedures/Assessments	Screening Visit[a]	ED1 (Baseline)[b]	Follow-Up Visits		End of Study Visit[c]
			6 ± 1 Weeks Following Baseline	Every 3 Months ± 2 Weeks Following Baseline	
Informed consent[d]	X				
Eligibility criteria	X				
Confirmation of eligibility		X			
Medical history[e]	X				
Medication history[f]	X				
Concomitant medications[g]		X	X	X	X
Non-drug therapies[g]	X	X	X	X	X
Physical examination[h]	X	X	X	X	X
Adverse events[g]		X	X	X	X
Laboratories[i]	X	X	X	X	X
Vital signs[j]	X	X	X	X	X
Bleeding episodes and their treatment[g]		X	X	X	X
Pregnancy test[k]	X				X
PROs[l]		X		X[m]	X
Patient e-diary[n]	X	X	X	X	X
IR determination		X	X	X	X
Dispense IP		X	X	X	

[a] The screening visit procedures, including laboratory evaluations, are to be completed within 45 days prior to the first infusion of BAX 855 on ED1.
[b] Determination of baseline incremental recovery with 60 ± 5 IU/kg of BAX 855.
[c] Including cases of withdrawal or discontinuation.
[d] Occurs at enrollment at latest (prior to any study-specific procedure).
[e] Medical history to include hemophilia history (confirmation of diagnosis & severity; family history of hemophilia; documentation of a mutation, if known; and presence of any target joints).
[f] Medication history to include documentation of all FVIII replacement therapies used within the last year, any prior history of use of any PEGylated medication (eg, PEG-interferon) at any time in the past, and other medications in the last 30 days.

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[g] Indicates that concomitant medications, non-drug therapies, adverse events, and bleeding episodes and their treatment will be continuously reviewed and specifically assessed at these times by the study site and discussed with the subject.
[h] Physical examination to include a measurement of height (cm) (for subjects aged < 18 years at enrollment) and weight (kg) and performance score (Karnofsky or Lansky) at screening.
[i] For laboratory assessments, see Section 20.4.2.
[j] Vital signs to include body temperature (ºC), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg).
[k] A hCG urine pregnancy test will be done on all females of childbearing potential at the screening and end of study visit.
[l] PROs to include the following depending on patient age: bleed and pain severity using Haemo-SYM (≥ 18 years), HRQoL using SF-36 (≥ 14 years), HRQoL using PedsQL (< 14 years), patient satisfaction with treatment using the Satisfaction Questionnaire (all ages), and Patient Activity Level (all ages).
[m] In addition to the baseline and end of study visit, PROs will be assessed every 6 months following baseline.
[n] E-diaries will be given out at screening and will be used to document bleeds, treatment administered and response to BAX 855, untoward events, concomitant medications and health resource use data. E-diaries are reviewed and discussed with the subject at each study visit.

20.3.3 Subjects on PK-Tailored Prophylactic Treatment Regimen (Transitioning and BAX 855 Naïve Subjects)

Procedures/Assessments	Screening Visit[a]	PK Assessment[b]	Baseline/Start of Prophylaxis 6 ± 1 Weeks[c]	Follow-Up Visits		End of Study Visit[d]
				4 ± 1, 8 ± 1, 18 ± 2 Weeks Following Baseline	Every 3 Months ± 2 Weeks Following Baseline	
Informed consent[e]	X					
Eligibility criteria	X					
Confirmation of eligibility		X	T[b]			
Medical history[f]	T* / N					
Medication history[g]	T* / N					
Concomitant medications[h]	T* / N	X	X	X	X	X
Non-drug therapies[h]	T* / N	X	X	X	X	X
Physical exam[i]	T* / N	X	X	X	X	X
Adverse events[h]	T*	X	X	X	X	X
Laboratories[j]	T* / N	X	X	X	X	X
Vital signs[k]	T* / N	X	X	X	X	X
Bleeding episodes and their treatment[h]	T*	T	T	X	X	X
Pregnancy test[l]	X					X
PROs[m]			X		X[n]	X
Patient e-diary[o]	X	X	X	X	X	X
PK determination		X				
IR determination	T*[p]		X		X	X
Trough levels				X		
Dispense IP	T	X	X	X	X	

Abbreviations: T = transitioning subjects; N = BAX 855 naïve subjects; X = all subjects (transitioning, BAX855 naïve subjects and subjects who are already in the continuation study and have not yet undergone PK).

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[a] The screening visit procedures, including laboratory evaluations, are to be completed within 45 days prior to the infusion of BAX 855 at the PK assessment. The procedures/assessments marked with an asterisk (*) will be transcribed from the end of study visit of the previous BAX 855 study for transitioning subjects. However, the following assessments are not part of the end of study assessments of the previous BAX 855 study and must be performed at screening to ensure eligibility: Performance score (Karnofsky or Lansky), viral serology (see Section 20.4.3), and pregnancy test if female of childbearing potential. Additionally, for subjects transitioning from the surgery study (Study 261204), FVIII assays and lipid panel (see Section 20.4.3) should also be performed. **Note:** Subjects can decide at any time during the continuation study to receive a PK-tailored dosing regimen. For this purpose, all the study visits starting from the PK assessment, if needed, will apply, however, the screening visit is not applicable.

[b] PK assessment does not need to be performed in transitioning subjects who have already undergone a PK assessment in a previous BAX 855 study. For these subjects the baseline/start of prophylaxis visit will be the first visit after the screening visit and eligibility will be confirmed at this visit.

[c] Baseline/start of PK-tailored prophylaxis starts 6±1 week following either PK determination in case the patient has not undergone a PK in a previous BAX855 study or 6±1 week following screening if a PK is already available. This visit will then coincide with confirmation of eligibility.

[d] Including cases of withdrawal or discontinuation.

[e] Occurs at enrollment at latest (prior to any study-specific procedure). For transitioning subjects from other BAX 855 studies, to give the patient sufficient time to review the ICF, this document should preferably be provided prior to the end of study visit of the previous study.

[f] Medical history to include hemophilia history (confirmation of diagnosis & severity; family history of hemophilia; documentation of a mutation, if known; and presence of any target joints).

[g] Medication history to include documentation of all FVIII replacement therapies used within the last year, any prior history of use of any PEGylated medication (eg, PEG-interferon) at any time in the past, and other medications in the last 30 days.

[h] Indicates that concomitant medications, non-drug therapies, adverse events, and bleeding episodes and their treatment will be continuously reviewed and specifically assessed at these times by the study site and discussed with the subject.

[i] Physical examination to include a measurement of height (cm) (for subjects aged < 18 years at enrollment) and weight (kg) and performance score (Karnofsky or Lansky) at screening.

[j] For laboratory assessments, see Section 20.4.

[k] Vital signs to include body temperature (ºC), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg).

[l] A hCG urine pregnancy test will be done on all females of childbearing potential at the screening and end of study visit.

[m] PROs to include the following depending on patient age: bleed and pain severity using Haemo-SYM (≥ 18 years), HRQoL using SF-36 (≥ 14 years), HRQoL using PedsQL (< 14 years), patient satisfaction with treatment using the Satisfaction Questionnaire (all ages), and Patient Activity Level (all ages).

[n] In addition to the baseline and end of study visit, PROs will be assessed every 6 months following baseline.

[o] E-diaries will be given out at screening and will be used to document bleeds, treatment administered and response to BAX 855, untoward events, concomitant medications and health resource use data. E-diaries are reviewed and discussed with the subject at each study visit.

[p] For transitioning subjects, IR determination may be performed at screening as part of the end of study visit of the previous BAX 855 study.

20.4 Clinical Laboratory Assessments

20.4.1 Subjects Transitioning from Other BAX 855 Studies on Fixed Dose Prophylactic Treatment Regimen

Assessments[a]	Screening Visit[b]	Follow-Up Visits		End of Study Visit[d]
		6 ± 1 Week Following Screening[c]	Every 3 Months ± 2 Weeks Following Screening[c]	
FVIII pre-infusion[e]	*	P	P	P
FVIII post-infusion[e]	*	P	P	P
TGA pre-infusion (optional)		P	P	P
TGA post-infusion (optional)		P	P	P
VWF antigen (pre-infusion) (optional)		P	P	P
Immunogenicity assays[f]	*	P	P	P
Hematology[g]	*	W	W	W
CD4 count	W		W[h]	
Clinical chemistry[i]	*	S	S	S
Lipid panel[j]	*	S	S	S
Viral serology[k]	S			

Abbreviations: W = whole blood; P = plasma; S = serum.

[a] At all visits subjects must not be actively bleeding and a washout period of at least 84 to preferably 96 hours following the previous dose of BAX 855 should be observed for blood sampling. All laboratory tests will be performed at a central laboratory.

[b] The results of the laboratory assessments marked with an asterisk (*) will be obtained/transferred from the end of study visit of the previous BAX 855 study. For subjects transitioning from the surgery study (Study 261204), FVIII assays and lipid panel are not part of the end of study assessments of the surgery study and must be performed at screening.

[c] IR determination for FVIII activity, TGA and pre-infusion VWF only if eligibility confirmed.

[d] Including cases of withdrawal or discontinuation.

[e] FVIII tests are: 1-stage clotting FVIII activity, FVIII chromogenic activity, and FVIII antigen. Samples will be taken within 30 minutes before and 30 ± 15 minutes after infusion of 60 ± 5 IU/kg of BAX 855.

[f] Immunogenicity assays are: inhibitory antibodies to FVIII, binding antibodies to FVIII, BAX 855 and PEG, anti-CHO antibodies. For binding antibodies, both IgG and IgM antibodies will be measured.

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[g] Hematology includes: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelet count.
[h] CD4 count to be tested every 6 months in subjects who are HIV positive.
[i] Clinical chemistry includes: Sodium, potassium, chloride, bicarbonate, total protein, albumin, ALT, AST, total bilirubin, alkaline phosphatase, BUN, creatinine, and glucose.
[j] Lipid panel includes: cholesterol, VLDL, LDL, HDL, and triglycerides.
[k] Viral serology includes: HIV-1Ab, HIV-2 Ab, HBcAb, HBsAb, HBsAg, and HCVAb. Any HIV or HCV positive sample will be tested by PCR for viral titer.

20.4.2 BAX 855 Naïve Subjects on Fixed Dose Prophylactic Treatment Regimen

Assessments[a]	Screening Visit[b]	ED1 (Baseline)	Follow-Up Visits		End of Study Visit[c]
			6 ± 1 Week Following Baseline	Every 3 Months ± 2 Weeks Following Baseline[d]	
FVIII tests[d]	P				
FVIII pre-infusion		P	P	P	P
FVIII post-infusion		P	P	P	P
TGA pre-infusion (optional)		P	P	P	P
TGA post-infusion (optional)		P	P	P	P
VWF antigen (pre-infusion) (optional)		P	P	P	P
Immunogenicity assays[e]	P	P	P	P	P
Hematology[f]	W		W	W	W
CD4 count	W			W[g]	
Blood type[h]	W				
Genetics and HLA-genotype	P				
Clinical chemistry[i]	S		S	S	S
Lipid panel[j]	S		S	S	S
Viral serology[k]	S				

Abbreviations: W = whole blood; P = plasma; S = serum.

[a] At all visits subjects must not be actively bleeding and a washout period of at least 84 to preferably 96 hours following the previous dose of BAX 855 or at least 72 hours following the previous dose of another FVIII concentrate should be observed for blood sampling. All laboratory tests will be performed at a central laboratory.

[b] Laboratory assessments are to be completed within 45 days prior to the first infusion of BAX 855.

[c] Including cases of withdrawal or discontinuation.

[d] FVIII tests are: 1-stage clotting FVIII activity, FVIII chromogenic activity, and FVIII antigen. Samples will be taken within 30 minutes before and 30 ± 15 minutes after infusion of 60 ± 5 IU/kg of BAX 855.

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[e] Immunogenicity assays are: inhibitory antibodies to FVIII, binding antibodies to FVIII, BAX 855 and PEG, anti-CHO antibodies. For binding antibodies, both IgG and IgM antibodies will be measured.

[f] Hematology includes: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelet count.

[g] CD4 count to be tested every 6 months in subjects who are HIV positive.

[h] If historical data on blood group type is available, this may be recorded in the eCRF and blood type does not need to be measured.

[i] Clinical chemistry includes: Sodium, potassium, chloride, bicarbonate, total protein, albumin, ALT, AST, total bilirubin, alkaline phosphatase, BUN, creatinine, and glucose.

[j] Lipid panel includes: cholesterol, VLDL, LDL, HDL, and triglycerides.

[k] Viral serology includes: HIV-1Ab, HIV-2 Ab, HBcAb, HBsAb, HBsAg, and HCVAb. Any positive viral antibody test will be repeated using a new blood sample in case the positivity is not part of the medical history. Any HIV or HCV positive sample will be tested by PCR for viral titer.

20.4.3 Subjects on PK-Tailored Prophylactic Treatment Regimen (Transitioning and BAX 855 Naïve Subjects)

Assessments[a]	Screening Visit[b,c]	PK Assessment[d]	Baseline/ Start of Prophylaxis 6 ± 1 Weeks[e]	Follow-Up Visits		End of Study Visit[g]
				4 ± 1, 8 ± 1, 18 ± 2 Weeks Following Baseline[f]	Every 3 Months ± 2 Weeks Following Baseline	
FVIII tests[h]	P (N)					
FVIII pre-infusion	P (T*)	P	P	P	P	P
FVIII post-infusion	P (T*)	P	P		P	P
TGA pre-infusion[i]		P	P	P	P	P
TGA post-infusion[i]		P	P		P	P
VWF antigen (pre-infusion)[i]		P	P	P	P	P
Immunogenicity assays[j]	P (T* / N)	P (N)	P		P	P
Hematology[k]	W (T* / N)		W		W	W
CD4 count	W				W[l]	
Blood type[m]	W (N)					
Genetics and HLA-genotype	P (N)					
Clinical chemistry[n]	S (T* / N)		S		S	S
Lipid panel[o]	S (T* / N)		S		S	S
Viral serology[p]	S					

Abbreviations: W = whole blood; P = plasma; S = serum. T = transitioning subjects (* denotes that data are transcribed from end of study visit of the previous BAX 855 study for transitioning subjects. However, for subjects transitioning from the surgery study (Study 261204), FVIII assays and lipid panel are not part of the end of study assessments of the previous BAX 855 study and must be performed at screening); N = BAX855 naïve subjects.

[a] At all visits subjects must not be actively bleeding and a washout period of at least 84 to preferably 96 hours following the previous dose of BAX 855 or at least 72 hours following the previous dose of another FVIII concentrate should be observed for blood sampling. All laboratory tests will be performed at a central laboratory.

[b] Laboratory assessments are to be completed within 45 days prior to the first infusion of BAX 855 for BAX855 naïve subjects.

[c] For subjects transitioning from the pivotal study (Study 261201), there is an optional assessment of IR at screening (in some BAX 855 studies, IR is assessed at the end of study visit and the results can be transcribed).

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[d] PK assessment does not need to be performed in transitioning subjects who have already undergone a PK assessment in a previous BAX 855 study. For these subjects the baseline/start of prophylaxis visit will be the first visit after screening and eligibility will be confirmed at this visit. PK assessment for subjects aged ≥ 12 years: Pre- and post-infusion blood draws over a period of 96 hours following the infusion of 60 ± 5 IU/kg of BAX 855 within 30 minutes before infusion and 0.25, 3, 9, 32, 56, and 96 hours post-infusion; PK assessment for subjects aged < 12 years: Pre- and post-infusion blood draws over a period of 56 hours following the infusion of 60 ± 5 IU/kg of BAX 855 within 30 minutes before infusion and 0.25, 9, and 56 hours post-infusion.

[e] Baseline/start of PK-tailored prophylaxis starts 6 ± 1 weeks following either PK determination in case the patient has not undergone a PK assessment in a previous BAX855 study, or 6 ± 1 weeks following screening if a PK assessment is already available (this visit will then coincide with confirmation of eligibility).

[f] Only FVIII trough levels and TGA parameters (subjects ≥ 12 years) prior to the next prophylactic infusions are to be performed to determine whether the subjects remains at FVIII trough levels of a minimum of 3%.

[g] Including cases of withdrawal or discontinuation.

[h] FVIII tests are: 1-stage clotting FVIII activity, FVIII chromogenic activity, and FVIII antigen. Samples will be taken within 30 minutes before and 30 ± 15 minutes after infusion of 60 ± 5 IU/kg of BAX 855.

[i] The assessment of TGA parameters and determination of pre-infusion VWF antigen level are optional in subjects aged < 12 years.

[j] Immunogenicity assays are: inhibitory antibodies to FVIII, binding antibodies to FVIII, BAX 855 and PEG, anti-CHO antibodies. For binding antibodies, both IgG and IgM antibodies will be measured.

[k] Hematology includes: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelet count.

[l] CD4 count to be tested every 6 months in subjects who are HIV positive.

[m] If historical data on blood group type is available for BAX 855 naïve subjects, this may be recorded in the eCRF and blood type does not need to be measured.

[n] Clinical chemistry includes: Sodium, potassium, chloride, bicarbonate, total protein, albumin, ALT, AST, total bilirubin, alkaline phosphatase, BUN, creatinine, and glucose.

[o] Lipid panel includes: cholesterol, VLDL, LDL, HDL, and triglycerides.

[p] Viral serology includes: HIV-1Ab, HIV-2 Ab, HBcAb, HBsAb, HBsAg, and HCVAb. For BAX 855 naïve subjects, any positive viral antibody test will be repeated using a new blood sample in case the positivity is not part of the medical history. Any HCV positive sample will be tested by PCR for viral titer.

20.5 Karnofsky and Lansky Scores

Karnofsky and Lansky Scores for Performance Status		
	Karnofsky Score (Subjects Aged ≥ 16 Years)	**Lansky Score (Subjects Aged < 16 Years)**
Score	**Definition**	**Definition**
100	Normal, no complaints; no evidence of disease	Fully active, normal
90	Able to perform normal activity; minor signs or symptoms of disease	Minor restriction in physically strenuous play
80	Able to perform normal activity with effort; some signs or symptoms of disease	Active, but tires more quickly
70	Cares for self, unable to perform normal activity or to do active work	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance but is able to care for most of own needs	Up and around, but minimal active play; keeps busy with quieter activities
50	Requires considerable assistance and frequent medical care	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities
40	Disabled; requires special care and assistance	Mostly in bed; participates in quiet activities
30	Severely disabled; hospitalization indicated, although death not imminent	In bed; needs assistance even for quiet play
20	Very sick; hospitalization necessary; active supportive treatment required	Often sleeping; play entirely limited to very passive activities
10	Moribund; Fatal processes progressing rapidly	No play; does not get out of bed
0	Dead	Unresponsive

Source: Karnofsky et al.[15] and Lansky et al.[16]

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22. SUMMARY OF CHANGES

Protocol 261302: Amendment 7 2015 MAR 20
Replaces: Amendment 4: 2014 MAR 21

In this section, changes from the previous version of the Amendment 1, dated 2013 OCT 02, are described and their rationale is given.

1. **Throughout the document**
   Description of Change: Change of sponsor name/entity.
   Purpose for Change: Administrative.

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: BAX 855

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

PROTOCOL IDENTIFIER: 261302

CLINICAL TRIAL PHASE 3b

AMENDMENT 7: 2015 MAR 20 (GLOBAL)
Replaces: AMENDMENT 4: 2014 MAR 23 (GLOBAL)

ALL VERSIONS:
AMENDMENT 7: 2015 MAR 20 (GLOBAL)
AMENDMENT 6: 2015 MAR 20 (GERMANY)
AMENDMENT 5: 2014 JUL 09 (RUSSIA)
AMENDMENT 4: 2014 MAY 23 (GLOBAL)
AMENDMENT 3: 2014 MAR 21 (GERMANY)
AMENDMENT 2: 2013 OCT 22 (RUSSIA)
AMENDMENT 1: 2013 OCT 02 (GLOBAL)
Original: 2013 JUN 18 (GLOBAL)

OTHER ID(s)
NCT Number: NCT01945593
EudraCT Number: NCT01945593
IND NUMBER: 15299

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

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

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Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
Barbara Valenta-Singer, MD
PPD Clinical Development