CLINICAL STUDY PROTOCOL

PEGylated rFVIII (BAX 855)

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

Short Title: Phase 3b Continuation Study of the Safety and Efficacy of Prophylactic BAX 855 in PTPs with Severe Hemophilia A

PROTOCOL IDENTIFIER: 261302

CLINICAL TRIAL PHASE 3b

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Study Sponsor(s):

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1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

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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 12.2
- Assessment of AEs, Section 12.11

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	Phase 3b Continuation Study of the Safety and Efficacy of Prophylactic BAX 855 in PTPs with Severe Hemophilia A
STUDY PHASE	Phase 3b
PLANNED STUDY PERIOD	
Initiation	2013 OCT
Primary Completion	2016 DEC (100 exposure days [EDs])
Study Completion	2016 DEC (100 EDs)
Duration	The overall duration is approximately 36 months from study initiation to last subject last visit.
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
• To continue the evaluation of the safety and efficacy of prophylaxis with BAX 855 for the prevention and treatment of bleeding episodes in PTPs (children and adults from 0 to 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 (episodes not associated with trauma)	
Secondary Objective(s)	
Efficacy 1. To determine the total ABR (spontaneous and traumatic bleeding episodes) 2. To determine the rate of success of BAX 855 for treatment of breakthrough bleeding episodes 3. To characterize the success of BAX 855 for treatment of bleeding episodes by the number of BAX 855 infusions for treatment and the length of intervals between bleeding episodes 4. To determine total weight-adjusted consumption of BAX 855 for prophylaxis and for the treatment of bleeding episodes 5. To assess Health-Related Quality of Life (HRQoL) over time for subjects receiving BAX 855	

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

Exploratory Objective

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

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 in approximately 200 male children and adult PTPs (0 to 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 BAX 855 for prophylaxis based on their previous treatment regimen and outcome for at least 100 EDs (as accumulated across all BAX 855 studies). Other BAX 855 studies currently include the phase 2/3 pivotal study (Baxter clinical study 261201), surgery study (Baxter clinical study 261204), and pediatric PTP study (Baxter clinical study 261202).
Planned Duration of Subject Participation	The subject participation period is estimated to be approximately 6 to 36 months. All subjects will continue on study until a minimum of 100 EDs per subject has been achieved across all BAX 855 studies in which each subject participated. Following 100 EDs, subjects will be given the option to continue until the study is terminated.

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. Rate of success 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 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

Patient Reported Outcomes (PROs)

Changes from baseline in the following:

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

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, length of stay, days missed from work/school)

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION

Investigational Product(s)	**BAX 855** **Dosage form**: BAX 855 is formulated as a sterile, highly purified protein preparation in lyophilized form for intravenous (i.v.) infusion and is provided in single-dose vials, which may contain nominally 250, 500, 1000, and 2000 IU rFVIII/vial, along with a vial of diluent (2 or 5 mL sterile water for injection (SWFI) as available). **Dosage frequency**: The BAX 855 dosage and infusion frequency for the initial prophylaxis period will be based on the subject's treatment regimen and spontaneous ABR (sABR) outcome from previous BAX 855 studies, as follows: A. Any subject treated on-demand from the phase 2/3 pivotal study with a sABR > 0, any subject from the surgery study, and any BAX 855-naïve subject will be treated with a fixed dose of 45± 5 IU/kg twice weekly. B. Any subject treated on prophylaxis from the phase 2/3 pivotal study, any subject from the pediatric PTP study, and any subject from other BAX 855 studies with a sABR > 0 will be treated with 45 to 80 (± 5) IU/kg twice weekly. C. Any subject treated on prophylaxis or on-demand from the phase 2/3 pivotal study, any subject from the pediatric PTP study, and any subject from other BAX 855 studies with a sABR = 0 may be treated with 30 to 80 (± 5) IU/kg every 5 days (q5d). After each consecutive 6 months of treatment, the BAX 855 dosage and/or frequency of infusions may be adjusted based on the subject's sABR outcome as follows: A. Subjects achieving a sABR > 0 on a twice weekly dosing schedule will continue with 45 to 80 (± 5) IU/kg twice weekly. B. Subjects achieving a sABR = 0 on a twice weekly dosing schedule may switch to 30 to 80 (± 5) IU/kg q5d.

	C. Subjects achieving a sABR = 0 on a q5d dosing schedule may switch to 30 to 80 (± 5) IU/kg every 7 days (q7d). D. Subjects achieving a sABR ≤ 2 on a q5d or a q7d dosing schedule may continue on their current infusion frequency. E. Subjects achieving a 2 < sABR ≤ 4 on a q7d dosing schedule may switch back to 30 to 80 (± 5) IU/kg q5d. F. Subjects achieving a sABR > 2 on q5d or ABR > 4 on q7d may switch back to 45 to 80 (± 5) IU/kg twice weekly. From these recommended dosages and infusion frequencies, the investigator will determine the prescribed dosage (allowing ± 5 IU/kg for variation), whether or not the q5d or q7d infusion frequency will be employed, and whether or not the subject's regimen will change after each 6 months of treatment. **Mode of Administration**: intravenous bolus infusion
SUBJECT SELECTION	
Targeted Accrual	Approximately 250 PTP male subjects with severe hemophilia A.
Number of Groups/Arms/Cohorts	A single group of BAX 855 prophylaxis

Inclusion Criteria

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 and in countries where the pediatric PTP study is being conducted can only be enrolled in this continuation study after enrollment in the pediatric PTP study is closed.

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

1. Subject and/or legal representative has/have voluntarily provided signed informed consent.
2. Subject is from 0 to 75 years of age at screening.
3. Subject is male with severe hemophilia A (FVIII clotting activity < 1%) as confirmed by central laboratory at screening after at least a 72-hour washout period or a documented FVIII clotting activity < 1% (confirmation is only required for BAX 855 naïve subjects).
4. Subject has documented previous treatment with plasma-derived FVIII concentrates or rFVIII for ≥ 150 EDs.
5. Subject is currently receiving prophylaxis or on-demand therapy with FVIII.
6. Subject has a Karnofsky (see Section 20.3) or Lansky performance score of ≥ 60.
7. 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.
8. 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.
9. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects, those who meet **ANY** of the following criteria are not eligible for this study:

1. Subject has detectable FVIII inhibitory antibodies (≥ 0.4 BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening.
2. Subject has history of FVIII inhibitory antibodies (≥ 0.4 BU using the Nijmegen modification of the Bethesda assay or ≥ 0.6 BU using 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 alanine aminotransferase (ALT), as confirmed by central laboratory screening, or documented at a local laboratory within 6 months prior to screening, or a documented INR > 1.5]
6. Subject has severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening, or documented at a local laboratory within 6 months prior to screening.
7. 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.
8. 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.
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.

STATISTICAL ANALYSIS

Sample Size Calculation

In total, approximately 250 subjects will be enrolled in this study. This sample size is based on the sample size calculations of the other BAX 855 studies (including the phase 2/3 pivotal, surgery, pediatric PTP), as well as the guidance EMA/CHMP/BPWP/144533/2009.

Planned Statistical Analysis

Primary Analysis

The number and proportion (Clopper-Pearson exact 95% CI) of subjects who develop inhibitory antibodies to FVIII will be provided. Only the inhibitory antibodies developed after the first exposure to BAX 855 will be included in the analysis.

The primary 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.

Secondary Analyses

- The total ABR (spontaneous and traumatic bleedings) will be estimated and similarly described as the primary efficacy outcome.
- Rate of Success of BAX 855 for treatment of breakthrough bleeding episodes

Success will be defined as a rating of excellent or good using the efficacy rating scale for treatment of bleeding episodes, 24 hours after initiation of BAX 855 treatment for the bleeding episode.

Success proportion (95% CI) will be estimated within a general estimating equation (GEE) model framework. The model will account for the fixed effects of bleeding severity, and the random subject effect.

For the dependent variable (success: yes/no) a binomial distribution and a log link will be assumed, and for the subject effect (defined by a repeated statement) an independence correlation structure will be used to start the estimation. Estimated model parameter values and CI limits will then be back-transformed to the original scale by exponentiation.

- Number of BAX 855 Infusions Needed for the Treatment of Bleeding Episodes
  Frequency tables will be prepared for the number of infusions required for the treatment of a bleed. The median number of infusions (and nonparametric 95% CI) will be estimated.
- Time Intervals Between Bleeding Episodes
  The average time interval between 2 consecutive bleeding episodes will be computed for each subject. If a subject does not have any bleeding episode then the observation will be censored at the end of the follow-up time of the respective subject. The median (95% CI) of those average time intervals between 2 bleeding episodes will be estimated.
- Weight-Adjusted Consumption of BAX 855
  Consumption of BAX 855 will be summarized as average number of BAX 855 infusions and average weight-adjusted consumption of BAX 855 per month.
- Haemo-SYM
  Higher scores on the Haemo-SYM indicate worse symptom severity. Changes from Baseline to End of Treatment in the Haemo-SYM scores will be tested for statistical significance, using a Wilcoxon test for paired samples. Improvement in the Haemo-SYM pain subscale of at least 11 points decreasing will be considered a meaningful improvement (a 1 point change on each pain question). Number and proportion of subjects with meaningful improvement in the Haemo-SYM pain subscale will be tabulated.
- SF-36
  Lower scores on SF-36 indicate worse HRQoL. Changes from Baseline to End of Treatment in the SF-36 scores will be tested for statistical significance using a Wilcoxon test for paired samples. Improvement in the SF-36 scale of at least 3 points increasing will be considered a meaningful improvement. The number and proportion of subjects with meaningful improvement in SF-36 will be tabulated.

Safety Analysis

Frequency counts and percentages will be calculated for SAEs, occurrence of inhibitory and binding 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.

Interim Safety Reviews

The first interim safety review will be done when 35 subjects complete 6 months of BAX 855 treatment with 30 to 80 IU/kg q5d.

Descriptive statistics of ABR of this period will be provided, in addition, the number and percentage (95% CI) of subjects with ABR = 0 in this 6-month observation period will be provided.

The second interim safety review will be done when 20 subjects complete 6 months of BAX 855 treatment with 30 to 80 IU/kg q7d.

The analysis of this interim will be the same as the first interim safety review.

An additional safety review is planned upon completion of the phase 2/3 pivotal study.

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5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	annualized bleed rate
AE	adverse event
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
AUC	area under the curve
AUC(0-∞)	area under the plasma concentration curve from 0 to infinity
BAX 855	product code name for Baxter'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
DI	dose intensification
DMC	data monitoring committee
EC	ethics committee
ED	exposure day
ELISA	enzyme-linked immunoabsorbent assay
EMA	European Medicines Agency
FAS	full analysis set
FVIII	factor VIII
GCP	Good Clinical Practice
GEE	general estimating equation
GLM	general linear model
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

Abbreviation	Definition
HDL	high density lipoprotein
HIV	human immunodeficiency virus
h	hour(s)
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)
INR	international normalized ratio
IR	incremental recovery over time
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
PEG	polyethylene glycol
PK	pharmacokinetic(s)
PKFAS	pharmacokinetic full analysis set
PP	per protocol
PRO	patient reported outcomes
PTP	previously treated patient
q5d	Dose every five (5) days
q7d	Dose every seven (7) days
rFVIII	recombinant factor VIII

Abbreviation	Definition
SAE	serious adverse event
SAER	serious adverse event report
SD	standard deviation
SF-36	Short form-36 questionnaire
SIC	subject identification code
SWFI	sterile water for injection
T1/2	half life
Tmax	time to maximum concentration in plasma
US	United States
VAS	visual analog scale
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

BAX 855, a novel PEGylated full-length recombinant factor VIII (rFVIII) molecule, is intended for use as a long-acting FVIII replacement therapy for prophylaxis and for the treatment of bleeding episodes in patients with severe hemophilia A.

Currently, the management of severe hemophilia A includes on-demand treatment for bleeding episodes and/or prophylaxis to prevent bleeding episodes.[1; 2] The average half-life of current FVIII products is in the range of 12-14 h,[3; 4] thus, these prophylaxis regimens require infusion every other day or every 2-3 days based on the patient's individual pharmacokinetic (PK) profile.[5] BAX 855 may improve the treatment of hemophilia A by reducing the frequency of prophylaxis infusions while maintaining a similar therapeutic benefit to existing FVIII products, thereby improving patient convenience, compliance with therapy, and 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). Polyethylene glycol (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 prophylaxis treatment regimens in this continuation study (30 to 80 [± 5] IU/kg, twice weekly, every 5 days [q5d], or every 7 days [q7d]) have been developed to ensure that subjects maintain FVIII trough levels above 1%. The dosage and frequency of infusions are calculated based on the 1.4 to 1.5 fold extended half-life of BAX 855 compared with ADVATE and on FVIII trough level estimated from subjects' half-life and incremental recovery values in the phase 1 study (Baxter clinical study 261101). In this continuation study, treatment regimens may be further adjusted at 6-month intervals based on the subject's treatment outcome. In the BAX 855 phase 2/3 pivotal study (Baxter clinical study 261201), the pediatric PTP study (Baxter clinical study 261202),

and in other BAX 855 studies, subjects are treated on prophylaxis at 30 to 80 (± 5) IU/kg every 3 to 4 days. For this continuation study, if a subject achieves a spontaneous annualized bleed rate (ABR) = 0 in the prior 6 months of treatment, he may receive a lower infusion frequency of q5d. If this subject maintains a spontaneous ABR = 0 in 6 months of dosing q5d, he may receive a further reduced infusion frequency of q7d. The actual prescribed dosage and frequency of infusions will be at the discretion of the investigator. For BAX 855 naïve subjects, treatment will begin at 45± 5 IU/kg twice weekly and after 6 months, the regimen may be adjusted based on treatment outcome.

Subjects who were previously treated on-demand, may receive on-demand treatment before the first prophylaxis dose (ie, after screening). The on-demand treatment regimen (dosages ranging from 10 to 60 [± 5] IU/kg) is based on extensive previous experience from use of ADVATE (additional information can be found in the ADVATE IB). The dosing is further supported by preclinical PK and bleeding model studies as well as the phase 1 clinical study in subjects with severe hemophilia A, which investigated safety and PK following infusion of 30 and 60 IU/kg. The FVIII dosing is also aligned with recommendations in the EMA/CHMP/BPWP/144533/2009 guideline.[6] Doses as high as 60 ± 5 IU/kg may be used for the treatment of bleeding episodes 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-linked recessive, congenital bleeding disorder caused by deficient or defective coagulation 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.[7; 8]

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 male PTP subjects with severe hemophilia A, of any ethnic group, from 0 to 75 years of age, 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 (see the ADVATE IB). Children < 12 years of age will not be enrolled in this continuation study until enrollment in the BAX 855 pediatric PTP study has been completed. 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

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 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 two primary pharmacodynamic models in FVIII knock-out mice.

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

6.4.1 Findings from Clinical Studies

A phase 1, first-in-human study (261101) to assess the safety and PK of BAX 855 in PTPs from 18 to 65 years of age with severe hemophilia A with ≥ 150 EDs to FVIII products was conducted in Europe and Japan. Single dosages of 30 IU/kg and 60 IU//kg BAX 855 were compared to the same doses of ADVATE. Subjects were followed for 28 days after BAX 855 administration for safety, including adverse events (AEs) and changes in vital signs, clinical laboratory assessments, and immunogenicity.

A total of 24 subjects were enrolled; 19 were treated, of which 18 were evaluable for the 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. There were no thrombosis-associated events or allergic reactions. No deaths or other SAEs occurred, and none of the 11 non-serious AEs (all mild or moderate) were considered treatment-related. AEs 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 for PK. Based on the one-stage clotting assay, the mean $T_{1/2}$ (h) was longer for BAX 855 than for ADVATE in both Cohort 1 (13.60 h vs 9.90 h) and Cohort 2 (16.64 h vs 11.11 h). Other PK parameters also supported an improved PK profile for BAX 855 compared to ADVATE.

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

Refer to the BAX 855 IB for periodic updates from the other BAX 855 studies.

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

Any anticipated risks and benefits associated with administration of BAX 855 are described 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 for the prevention and treatment of bleeding episodes in PTPs (children and adults from 0 to 75 years of age) 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 ABR of spontaneous bleeding episodes (ie, episodes not associated with trauma)

7.3 Secondary Objectives

7.3.1 Efficacy

1. To determine the total ABR (spontaneous and traumatic bleeding episodes)
2. To determine the rate of success of BAX 855 for the treatment of breakthrough bleeding episodes
3. To characterize the success of BAX 855 for treatment of bleeding episodes based on the number of BAX 855 infusions for the treatment and the length of intervals between bleeding episodes
4. To determine total weight-adjusted consumption for prophylaxis and for the treatment of bleeding episodes
5. To assess Health-Related Quality of Life (HRQoL) 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

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

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 in approximately 250 male children and adult PTPs (0 to 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 BAX 855 for prophylaxis based on their previous treatment regimen and spontaneous ABR outcome for at least 100 EDs (as accumulated across all BAX 855 studies).

8.2 Overall Study Design

Subjects who complete treatment and assessments in the other BAX 855 studies (phase 2/3 pivotal, surgery, and/or pediatric PTP studies), as well as BAX 855-naïve subjects, and who fulfill the inclusion/exclusion criteria will be eligible to participate in this continuation study. Approximately 250 male 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 recommendations for the study of FVIII in severe hemophilia A.[6]

The subject's hemophilia history, bleeding episode history, and FVIII usage and treatment regimen(s) within the previous year will be collected at screening. 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 will receive BAX 855 for in-home prophylaxis with the treatment regimen dependent on their previous regimen and spontaneous ABR outcome (as described in Section 8.6.3). 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 8.6.3.1 and Table 3) will be recorded in an electronic diary (e-diary). If the BAX 855 treatment response is inadequate, ADVATE may be used for rescue therapy. Subjects will be treated with BAX 855 for a minimum of 100 EDs (accumulated across all BAX 855 studies they have participated in). After 100 EDs, subjects will the option to continue in this study until the sponsor terminates it.

Subjects will return to the study site at follow-up visits (at 6 weeks and every 3 months) after the first prophylactic infusion for safety assessments and for review of

their e-diaries. Investigators will review e-diaries for untoward events, concomitant medications, non-drug therapies, and patient reported outcomes (PROs; see Section 10.3.5). 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 BU), or who develop a low responder inhibitor (≤ 5 BU but ≥ 0.4 BU) that cannot be adequately managed by the prescribed prophylaxis regimen with BAX 855 will be discontinued from study.

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 approximately 36 months from study initiation (ie, first subject enrolled by signing informed consent) to study completion (ie, last subject last visit). Recruitment will continue until the last subject has completed any other BAX 855 study that the sponsor considers as having potential subjects for this continuation study.

The initiation date and the completion date will vary for each subject depending on the BAX 855 study he participated in or if he is BAX 855 naïve. The subject participation period is estimated to be approximately 6 to 36 months and is dependent on the subject receiving a minimum of 100 EDs with BAX 855 (as accumulated across all BAX 855 the subject has participated in). Following 100 EDs, subjects will be given the option to continue until the study is terminated.

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. Rate of success 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 72-hour washout period is required)
   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 the following:

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

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, length of stay, days missed from work/school)

8.4.4 Randomization and Blinding

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

8.5 Study Stopping Rules

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

- 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:

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

8.6 Investigational Product(s)

8.6.1 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 condition for BAX 855 is 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.

8.6.2 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.

8.6.3 Description of Treatment

Subjects will be treated on specified prophylaxis treatment regimens for 6-month periods until they reach 100 EDs (accumulated across all studies). The BAX 855 regimen (dosage and frequency of infusions) will be determined based on the subject's previous treatment regimen and spontaneous ABR (sABR) outcome as follows (also refer to Table 1):

A. Any subject treated on-demand from the phase 2/3 pivotal study with a sABR > 0, any subject from the surgery study, and any BAX 855-naïve subject will be treated with a fixed dose of 45± 5 IU/kg twice weekly.
B. Any subject treated on prophylaxis from the phase 2/3 pivotal study, any subject from pediatric PTP study, and any subject from other BAX 855 studies with an sABR > 0 will be treated with 45 to 80 (± 5) IU/kg twice weekly. The investigator will determine prescribed dosage with a ± 5 IU/kg allowance.
C. Any subject treated on prophylaxis or on-demand from the phase 2/3 pivotal study, any subject from the pediatric PTP study, and any subject from other BAX 855 studies with an sABR = 0, may be treated, at the investigator's discretion, with 30 to 80 (± 5) IU/kg q5d. The investigator will determine prescribed dosage with a ± 5 IU/kg allowance.

After each consecutive 6 months of treatment, the BAX 855 dosage and/or frequency of infusions may be adjusted based on the subject's estimated sABR for the previous period as follows (also refer to Table 1):

A. Subjects achieving a sABR > 0 on a twice weekly dosing schedule will continue with 45 to 80 (± 5) IU/kg twice weekly.
B. Subjects achieving aABR = 0 on a twice weekly dosing schedule may switch to 30 to 80 (± 5) IU/kg q5d, at the investigator's discretion.
C. Subjects achieving a sABR = 0 on a q5d dosing schedule may switch to 30 to 80 (± 5) IU/kg q7d, at the investigator's discretion.
D. Subjects achieving a sABR ≤ 2 on a q5d or a q7d dosing schedule may continue on their current dosage and infusion frequency, at the investigator's discretion.
E. Subjects achieving a 2 < sABR ≤ 4 on a q7d dosing schedule may switch back to 30 to 80 (± 5) IU/kg q5d, at the investigator's discretion.
F. Subjects achieving an sABR > 2 on q5d or ABR > 4 on q7d may switch back to 45 to 80 (± 5) IU/kg twice weekly, at the investigator's discretion.

From these recommended dosages and infusion frequencies, the investigator will determine the prescribed dosage (allowing ± 5 IU/kg for variation), whether or not the

q5d or q7d infusion frequency will be employed, and whether or not the subject's regimen will change after each 6 months of treatment.

Table 1
BAX 855 Dosage and Infusion Frequency Schedule and Recommended Adjustments

Subjects	0-6 Months	6-12 Months	12-18 Months	≥18 Months
Subjects treated on-demand subjects from the phase 2/3 pivotal with sABR > 0 Subjects from the surgery study BAX 855 naïve subjects	Fixed dose: 45 ± 5 IU/kg twice weekly	sABR > 0: 45 to 80 (± 5) IU/kg[a] twice weekly	sABR > 0: 45 to 80 (± 5) IU/kg[a] twice weekly	sABR > 0: 45 to 80 (± 5) IU/kg[a] twice weekly
		sABR = 0: 30 to 80 (± 5) IU/kg[a] q5d[b]	sABR > 2: 45 to 80 (± 5) IU/kg[a] twice weekly	
			sABR ≤ 2: 30 to 80 (± 5) IU/kg[a] q5d[b]	
			sABR = 0: 30 to 80 (± 5) IU/kg[a] q7d[b]	sABR > 4: 45 to 80 (± 5) IU/kg[a] twice weekly
				2 < sABR ≤ 4: 30 to 80 (± 5) IU/kg[a] q5d[b]
				sABR ≤ 2: 30 to 80 (± 5) IU/kg[a] q7d[b]

Table 1
BAX 855 Dosage and Infusion Frequency Schedule and Recommended Adjustments

<table>
<tr><th>Subjects</th><th>0-6 Months</th><th>6-12 Months</th><th>12-18 Months</th><th>≥18 Months</th></tr>
<tr><td>Subjects from the phase 2/3 pivotal study</td><td>sABR > 0:
45 to 80 (± 5) IU/kg[a]
twice weekly</td><td>sABR > 0:
45 to 80 (± 5) IU/kg[a]
twice weekly</td><td>sABR > 0:
45 to 80 (± 5) IU/kg[a]
twice weekly</td><td>sABR > 0:
45 to 80 (± 5) IU/kg[a]
twice weekly</td></tr>
<tr><td rowspan="4">Subjects from the, pediatric PTP study

Subjects from other BAX 855 studies</td><td rowspan="4">sABR = 0:
30 to 80 (±5) IU/kg[a]
q5d[b]</td><td>sABR > 2:
45 to 80 (± 5) IU/kg[a]
twice weekly</td><td colspan="2" rowspan="2"></td></tr>
<tr><td>sABR ≤ 2:
30 to 80 (± 5) IU/kg[a]
q5d[b]</td></tr>
<tr><td rowspan="3">sABR = 0:
30 to 80 (± 5) IU/kg[a]
q7d[b]</td><td>sABR > 4:
45 to 80 (± 5) IU/kg[a]
twice weekly</td><td rowspan="3"></td></tr>
<tr><td>2 < sABR ≤ 4:
30 to 80 (± 5) IU/kg[a]
q5d[b]</td></tr>
<tr><td>sABR ≤ 2:
30 to 80 (± 5) IU/kg[a]
q7d[b]</td></tr>
</table>

Abbreviations: sABR = spontaneous annualized bleed rate; PTP = previously treated patients; q5d = every 5 days; q7d = every 7 days.

[a] From the recommended dosage range, the investigator will determine prescribed dosage, allowing ± 5 IU/kg.

[b] Infusion frequencies of q5d or q7d will be at investigators discretion.

A subject may receive a BAX 855 dosage < 45 IU/kg if he has a known PK profile from another BAX 855 study that will maintain his FVIII trough level above 1%.

For subjects receiving twice weekly prophylaxis and with spontaneous ABR > 2, dosing of BAX 855 may, for a 6-month period target, a FVIII trough level of up to 10%, at investigators' discretion and with approval by the sponsor's medical director.

Subjects meeting any of the following criteria during prophylaxis may have their BAX 855 dosage and/or infusion frequency increased before completion of the 6-month treatment period:

- 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 dose adjustment may take place only after consultation with the sponsor's medical director and written documentation of the decision, which will be recorded in the eCRF. The BAX 855 dosage may be increased gradually up to a maximum of 80 ± 5 IU/kg and/or the frequency of infusions can be changed to twice weekly.

8.6.3.1 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 2. 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 2). The subject or their caregiver will rate the severity (mild, moderate, or severe) of the bleeding episode and will rate the overall treatment response at 24 hours (± 2 hours) after initiating treatment. A 4-point efficacy rating scale (Table 3) will be used to assess the efficacy of BAX 855 treatment. Efficacy will not be assessed if ADVATE or any other FVIII concentrate is administered for the treatment of bleeding episodes. Efficacious treatment will be defined as a response of good or excellent. As described in Table 3, multiple infusions of BAX 855 may be administered for the treatment of a bleeding episode.

When bleeding is controlled, additional infusions of BAX 855 to maintain hemostasis (FVIII trough levels of 1%) is permitted, if required, for a maximum of 24 hours after resolution of bleeding or the subject can return to his prophylaxis regimen. Infusions to maintain hemostasis will count as EDs.

Table 2
BAX 855 and ADVATE Treatment Guidelines for Bleeding Episodes

Type of Bleeding Episode	Dose	Frequency of Dosing
Minor Early hemarthrosis, mild muscle bleeding, or mild oral bleeding, including, epistaxis	10 to 20 (±5) IU/kg	Repeat infusions every 12 to 24 h for 1 to 3 days until the bleeding episode is resolved
Moderate Moderate bleeding into muscles, bleeding into the oral cavity, definite hemarthroses, and known trauma	15 to 30 (±5) IU/kg	Repeat infusions every 12 to 24 h for 3 days or more until the pain and moderate 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	30 to 60 (±5) IU/kg	Repeat infusions every 8 to 12 h until the bleeding episode is resolved

NOTE: Subjects with life-threatening or gastrointestinal bleeding should be withdrawn from the study.

Table 3
Efficacy Rating Scale for Treatment of Bleeding Episodes at 24 ± 2 Hours from the Initiation of Treatment

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.

8.6.3.2 Immune 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 ≥ 0.4 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 ITI 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.

8.6.4 Treatment for Surgery or Dental Procedures

Subjects enrolled in this continuation study who require elective surgery may be eligible to enroll in the BAX 855 surgery study (Baxter clinical study 261204) if it is open for enrollment. Following an invasive or surgical procedure and completion of the surgery study, subjects may be eligible to return to this continuation study when they are able to resume a prophylaxis regimen and with the sponsor's medical director approval. Upon return to this study, these subjects will receive the treatment regimen corresponding to the beginning of the study (45 to 80 [± 5] IU/kg twice weekly for 6 months).

Subjects from this continuation study who participate in the surgery study will continue to receive their continuation study BAX 855 treatment during the following periods in the surgery study:

1. From the screening visit to the pre-surgical PK assessment,
2. From completion of the pre-surgical PK assessment to initiation of the pre-operative procedures, and
3. From hospital discharge following the surgery to the end of study visit.

During these periods, subjects will maintain their e-diaries for the continuation study, the continuation study investigator will be responsible for the subject's safety and treatment, and any data collected will be part of this continuation study.

During the pre-surgery PK assessment and from the initiation of the pre-operative procedures to the end of the surgery study's treatment plan, subjects will receive BAX 855 from the surgery study, and any data collected will be part of the surgery study.

Subjects who require any emergency surgery will be withdrawn from this continuation study.

8.6.5 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

disposition. IP must be dispensed only at the study site or other suitable location (e.g. infusion center; home, as applicable per study design), as specified in the protocol. 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 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.

8.7 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 CRFs refer to Section 17.2. The use of subject diaries is described in Section 10.5.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects 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 weeks of the previous study end of study visit to confirm eligibility for this continuation study.

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 and in countries where the pediatric PTP study

is being conducted can only be enrolled in this continuation study after enrollment in the pediatric PTP study is closed.

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

1. Subject and/or legal representative has/have voluntarily provided signed informed consent.
2. Subject is from 0 to 75 years of age at screening.
3. Subject is male with severe hemophilia A (FVIII clotting activity < 1%) as confirmed by central laboratory at screening (after at least a 72-hour washout period) or a documented FVIII clotting activity <1% (confirmation is only required for BAX 855 naïve subjects).
4. Subject has documented previous treatment with pd FVIII or rFVIII concentrates for ≥ 150 EDs.
5. Subject is currently receiving prophylaxis or on-demand therapy with FVIII.
6. Subject has a Karnofsky (see Section 20.3) or Lansky performance score of ≥ 60.
7. 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.
8. 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.
9. Subject is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

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

1. Subject has detectable FVIII inhibitory antibodies (≥ 0.4 BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening.
2. Subject has history of FVIII inhibitory antibodies (≥ 0.4 BU using the Nijmegen modification of the Bethesda assay or ≥ 0.6 BU using 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 alanine aminotransferase (ALT), as confirmed by central laboratory at screening, or documented at a local laboratory within 6 months prior to screening, or a documented INR > 1.5].
6. Subject has severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening, or documented at a local laboratory within 6 months prior to screening.
7. 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.
8. Subject has participated in another clinical study involving an investigational product (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.
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.

9.3 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 CRF. Assessments to be performed at the end of study visit (including in cases of withdrawal or discontinuation) are described in Section 10.3.4.

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 discontinue 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 ≥ 0.4 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 extensive FVIII replacement therapy.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (ie, signs and dates the ICF 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, CRFs, 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. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The procedures to be performed at each study visit, including screening, can be found in Supplement 20, Schedule of Study Procedures and Assessments, and Supplement 20.2, Clinical Laboratory Assessments.

Subjects will participate in each of the following study visits:

- Screening visit (exception: subjects transitioning from other BAX 855 studies who have completed end of study assessments that match assessments required for this continuation study screening visit; see Section 10.3.1 for details)
- Start of prophylaxis visit
- Follow-up visits at the study site at 6 weeks (- 1 or + 2 weeks) and every 3 months (± 4 weeks) after the start of prophylaxis
- End of study visit

10.3.1 Screening Visit

The screening visit procedures, including laboratory assessments, must be completed within 45 days prior to the first infusion of BAX 855, or repeated if more than 45 days have elapsed.

Subjects transitioning from the phase 2/3 pivotal, surgery, pediatric PTP, or another BAX 855 study, can use the end of study assessments in their prior study for screening visit assessments in this continuation study. Any additional required screening assessments will be performed at the screening visit in this continuation study within 2 weeks of completion of the previous study. Subjects will return to the study site no later than 6 weeks after the end of study visit in their prior study to confirm eligibility.

Subjects treated only with BAX 855 during the 4 weeks prior to the screening visit will be supplied with BAX 855 for a maximum of 6 weeks for prophylaxis treatment based on their previous treatment regimen and ABR outcome as described in Section 8.6.3.

Subjects using FVIII concentrates other than BAX 855 during the 4 weeks prior to the screening visit, will be offered ADVATE (to continue their treatment of bleeding episodes and prophylaxis) until the start of prophylaxis visit.

As a guideline of the screening assessments, Table 4 compares the end of study assessments from the other BAX 855 studies with assessments in this continuation study.

Table 4
Comparison of End of Study Assessments from the Other BAX 855 Studies (Phase 2/3 Pivotal, Surgery, and Pediatric PTP) and Screening Assessments from this Continuation Study

Assessment	Other BAX 855 Studies End of Study Assessments	Continuation Study Screening Assessments
Informed consent		X
Eligibility criteria		X
Medical history[a]		X
Medication history[a]		X
Concomitant medications[a]	X	X
Non-drug therapies	X	X
Physical examination[a]	X	X
Vital signs[a]	X	X
Adverse events	X	X
On study bleeding episodes and their treatment[b]	X	
Bleeding episodes and their treatment[a]	X[a]	X
Hematology[a]	X	X
Clinical chemistry[a]	X	X
Lipid Panel[a]	X	X
Immunogenicity assays[c]	X	X
FVIII/VWF assays	X[d]	X[e]
Viral serology[a]	X[f]	X
Blood group[g]		X
Patient e-diary[a]		X

[a] Refer to Section 20 and Section 20.2 for more details. It is not necessary to repeat assessments at this continuation study screening visit if they are completed at the end of study visit in another BAX 855 study.
[b] Record of bleeding episodes and their treatment since last study visit in the prior BAX 855 study.
[c] Immunogenicity assessments include: inhibitory antibodies to FVIII, binding antibodies to FVIII, BAX 855 and PEG, and anti-CHO antibodies. Both IgG and IgM binding antibodies are measured. A 72-hour washout period is required.

[d] FVIII/VWF assays include: 1-stage clotting FVIII activity, FVIII chromogenic activity, FVIII antigen, and VWF antigen at pre-infusion time points only.
[e] FVIII assays (only) include 1-stage clotting FVIII activity, FVIII chromogenic activity, and FVIII antigen.
[f] Performed at the end of study visit in the surgery study.
[g] Blood group (A, B, AB or O) if historical data not available.

For BAX 855 naïve patients, the following screening assessments will be performed after at least a 72-hour washout:

- Assessment of inclusion/exclusion criteria
- Clinical assessments:
  - 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.
  - Bleeding history and treatment
  - All FVIII replacement therapies used within the last year will be documented, 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
    - Usual response to treatment for bleeding episodes
    - Assessment of subject's ABR over prior 3-6 months, based on subject's own diary or recall
  - Concomitant medications for 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
  - Current non-drug therapies
  - Physical exam including height (cm) (for subjects less than 18 years of age at enrollment) and weight (kg)

- Vital signs (body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg).

- Laboratory Assessments:
  - FVIII assays:
    - FVIII activity
      - 1-stage clotting assay
      - Chromogenic assay
    - FVIII antigen
  - Immunogenicity tests (a 72-hour washout period is required):
    - Inhibitory antibodies to FVIII (Nijmegen assay)
    - Binding antibodies (IgG and IgM) to FVIII, BAX 855, PEG
    - Anti-CHO antibodies
  - Hematology, clinical chemistry, and lipid panel
  - Blood group (A, B, AB or O) if historical data not available; if available, historical data will be recorded on the CRF.
  - Viral serology, including:
    - HIV: HIV-1 and HIV-2 Ab
    - HBV: HBsAg, HBsAb, HBcAb
    - HCV: HCVAb
- E-diary distribution

Any positive viral serology test will be confirmed at the central laboratory with a new blood sample. HCV titer will be measured by PCR for subjects that are HCV positive.

10.3.2 Start of Prophylaxis Visit

At the start of prophylaxis visit, baseline assessments will be preformed prior to the first prophylactic dose of BAX 855. However, subjects transitioning from other BAX 855 studies who receive the first infusion BAX 855 at the screening visit will not have a start of prophylaxis visit.

The following baseline assessments will be completed up to 7 days before the first infusion of BAX 855 and with at least a 72-hour washout:

- Physical examination, including height (for subjects < 18 years of age at enrollment) and weight and vital signs
- Hematology, clinical chemistry, and lipid panel

- FVIII assays
- Immunogenicity assays (a 72-hour washout period is required)
- AEs occurring between screening and start of prophylaxis visit
- Concomitant medications
- Non-drug therapies
- All bleeding episodes and their treatment between screening and start of prophylaxis visit
- Patient Reported Outcomes (PROs; as described in Section 10.3.5)
- Review of subject's diary

10.3.3 Follow-up Visits (at 6 Weeks and Every 3 Months)

Follow-up visits will be performed at 6 weeks (- 1 or + 2 weeks) and every 3 months (± 4 weeks) after the start of prophylaxis. The follow-up visits must be scheduled so that blood sampling is prior to planned the BAX 855 infusion in order for the FVIII measurements to be used as an estimate of FVIII trough level and FVIII peak level is 30 ± 15 minutes after the BAX 855 infusion. The following assessments will be performed after at least a 72-hour washout:

- Physical examination, including height (for subjects less than 18 years of age at enrollment), weight, and vital signs
- Hematology, chemistry chemistry, and lipid panel
- FVIII assays: blood sampling before and 30 ± 15 minutes after the BAX 855 infusion
- Immunogenicity assays (a 72-hour washout period is required)
- Continuous monitoring for AEs and Concomitant medications
- Non-drug therapies
- All bleeding episodes and their treatment from first prophylaxis dose of BAX 855 will be documented
- Review of subject's diary
- At each consecutive 6 months visit, the ABR must be estimated and dose regimen may be revised (refer to Section 8.6.3)

10.3.4 End of Study Visit

The following end of study visit assessments will be performed 28 days ± 2 weeks after the last infusion of BAX 855 and at least a 72-hour washout:

- Physical examination including height (for subjects less than 18 years of age at enrollment), weight, and vital signs
- Non-drug therapies
- Hematology, chemistry, lipid panel
- FVIII assays
- Immunogenicity assays (a 72-hour washout period is required)
- Continuous monitoring for AEs and concomitant medications
- All bleeding episodes and their treatment from last dose of BAX 855 until study termination
- PROs (as described in Section 10.3.5)
- Review of subject's diary

10.3.5 Patient Reported Outcomes (PROs)

PROs will be administered at the start of prophylaxis visit (baseline) and 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.

The following PROs will be assessed at the start of prophylaxis and end of study visits:

- Bleed and pain severity will be measured using the Haemo-SYM for subjects ≥ 18 years of age
- HRQoL will be assessed using the SF-36 for subjects ≥ 14 years of age
- Patient satisfaction with treatment will be assessed using the Satisfaction Questionnaire (for subjects ≥ 12 years of age, the subject completes the questionnaire; for subjects < 12 years of age, the caregiver completes it on behalf of the subject)
- Patient Activity Level (for subjects ≥ 12 years of age, the subject completes the assessment; for subjects < 12 years of age, the caregiver completes it on behalf of the subject)

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. This questionnaire will be administered only to subjects ≥ 18 years of age at enrollment)
- **Short Form-36 (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. This questionnaire will be administered only to subjects ≥ 14 years of age and
- **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, 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. For subjects ≥ 12 years of age at enrollment, the subject completes the questionnaire and for subjects < 12 years of age at enrollment, the caregiver completes it on behalf of the subject.
- **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. For subjects ≥ 12 year of age at enrollment, the subject completes the assessment and for subjects < 12 years of age at enrollment, the caregiver completes it on behalf of the subject.

In addition, the following will be collected <u>where applicable, for each occurrence</u>:

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

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
- Any FVIII other than BAX 855 or ADVATE (during the course of the study)

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

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

- Medications:
  - ADVATE, provided by the study site, is permitted for:
    - Treatment of bleeding episodes and prophylaxis following enrollment until first prophylactic dose of BAX 855
    - During the observation period between the last follow-up visit and end of study visit
    - Rescue therapy for bleeding episodes that do not respond to BAX 855 during the study
    - Any ADVATE taken, regardless of whether it is provided by the study site or not, will be documented.
  - 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

10.5 Subject Diary

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

- Infusion record for BAX 855
- Infusion record for ADVATE
- Details of bleeding episodes and response to treatment
- Untoward events
- Concomitant medications (including immunizations) and non-drug therapies
- PROs

Subjects and/or their legally authorized representatives will be trained on use of the diary during the screening visit. Diaries will be provided in electronic form 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 diary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the eCRF by a validated transfer.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he 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).

Subjects have the option to exit the study once they have completed 100 EDs with BAX 855. Subjects can continue for an additional 50 EDs, or until the sponsor deems the BAX 855 study complete.

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, 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, 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 Schedule of Study Procedures and Assessments and Supplement 20.2, 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. 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 Rate of Success of BAX 855 for Treatment of Bleeding Episodes

The key secondary measure of efficacy is the rate of success of BAX 855 to treat bleeding episodes. Success will be determined by the subject or subject's caregiver. If the bleeding episode is managed in the clinic/hospital, the efficacy rating may be performed by the investigator. BAX 855 efficacy will be evaluated for each bleeding episode and will be assessed 24 hours (± 2 h) after initiating treatment using the efficacy rating scale (Table 3). Success is defined as a response of excellent or good at 24 hours post-infusion.

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, his caregiver, and/or investigator, and is based upon the subject's response to treatment, using the efficacy rating scale in Table 3. 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, his caregiver, and/or investigator will determine when a bleeding episode has occurred (see Section 11.1 above). The time interval will be defined as the date/time from when a recent bleed is stopped to the start day/time of the next bleeding episode.

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

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.

12.2 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). 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 ≥ 0.4 BU, as measured by the Nijmegen assay modification of the Bethesda assay
- Severe hypersensitivity/allergic reactions to BAX 855

12.3 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.

12.4 Non-Serious Adverse Event

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

12.5 Severity

Subjects transitioning from a prior BAX 855 study who experienced an AE that has not been 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.

12.6 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 related to 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.

12.7 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.

Preexisting diseases that are present before entry in to the study are described in the medical history, and 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, frequency, or duration of a preexisting disease, the event must be described on the AE CRF.

12.8 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 CRF.

12.9 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, for all subjects, 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 and on the AE CRF. 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 CRF; these events will not be considered as AEs and will not be included in the analysis of AEs.

12.10 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 (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 will be returned to the sponsor for inspection and analysis according to procedures.

12.11 Assessment of Adverse Events

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 clinic visits for administration of BAX 855
- Hospitalization for routine bleeding episode management that could be managed in the clinic 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 in-patient hospitalization or emergency room visit/admittance (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 (epistaxis, gastrointestinal bleeding, musculoskeletal bleeding) are part of the underlying disease, and therefore, are not reported as AEs; they will be evaluated in the context of efficacy. If a bleeding episode was caused by an injury, 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). 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.

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

For the purposes of this study and for all subjects, 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 CRF; these events are considered to be untoward medical occurrences and will not be considered as AEs and will not be included in the analysis of AEs.

Each AE from the first IP exposure in this continuation study until study completion/discontinuation date will be recorded on the AE CRF 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 12.4). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.5
- Severity as defined in Section 12.8
- Causal relationship to IP exposure as defined in Section 12.9

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.

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 CRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first.

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 (interim) medical history.

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.

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 CRFs is necessary.

12.12 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (mild, moderate, or severe as defined in Section 12.8). Medical history including surgery will include the following body systems, along with start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; 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 CRFs.

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 CRF.

12.13 Physical Examinations

At screening and subsequent study visits (as described in Section 20), a physical examination will be performed on the following body systems being described as normal or abnormal: 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 CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.10), 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.

12.14 Clinical Laboratory Parameters

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

12.14.1 Hematology, Clinical Chemistry, and Lipid Panel

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.

Blood will be obtained for assessment of hematology, clinical chemistry and lipid parameters at the screening visit, start of prophylaxis visit, follow-up visits, and end of study visit. Hematology, clinical chemistry and lipid assessments will be performed on EDTA-anticoagulated whole blood and serum, respectively, at the central laboratory.

12.14.2 Blood Type

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

12.14.3 Factor VIII Activity and Antigen

FVIII activity will be measured using the one-stage clotting assay and the chromogenic assay. FVIII antigen will be measured using an ELISA assay. Blood will be obtained for the FVIII assessments at the screening visit, start of prophylaxis visit, follow-up visits, and end of study visit.

12.14.4 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 at least a 72-hour washout period at the screening, follow-up and end of study visits. A 72-hour washout period is recommended prior to an unscheduled test.

A low titer (responder) inhibitor is defined as ≤ 5 BU but ≥ 0.4 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.

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.

Blood will be obtained for these assessments at the screening visit, start of prophylaxis visit, follow-up visits, and end of study visit.

12.14.5 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. Any positive test will be repeated using a new blood sample.

12.14.6 Assessment of Laboratory Values

12.14.6.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each abnormal standard clinical laboratory value (ie, hematology, clinical chemistry and lipids) is to be recorded on the CRF. 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 a new AE (see definition in Section 12.4 and record the sign, symptom, or medical diagnosis on the AE CRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.4), 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 was due to a preexisting disease (described in Section 12.7), due to a lab error, due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, 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 human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) shall be re-tested.

12.14.7 Biobanking

Backup samples should be taken 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.

Back-up samples are planned at the screening, start of prophylaxis, follow-up, and end of study visits, and will be stored appropriately. This will ensure that there is sufficient material should any results require a re-test or additional testing (eg, further evaluation of an abnormal test or an AE).

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.

12.15 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 sitting position.

Vital sign values are to be recorded on the CRF. 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 CRF). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE CRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, 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 the sample size calculations of the other BAX 855 studies (including the phase

2/3 pivotal, surgery, pediatric PTP), as well as the guideline 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 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.

13.3 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 who develop inhibitory antibodies to FVIII will be provided. Only the inhibitory antibodies developed after the first exposure to BAX 855 will be included in the analysis, the inhibitory antibodies developed before the first exposure to BAX 855 will be listed separately.

13.4.1.2 Primary Efficacy Outcome Measure

The primary outcome measure, the spontaneous ABR, will be assumed to have a negative binomial distribution, 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), treatment regimen as a fixed effect and 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 Total ABR

The mean total ABR (spontaneous and traumatic bleeding episodes) (95% CI) will be estimated and described similarly as the primary efficacy outcome, using a general estimating equation (GEE) model with 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.

13.4.2.2 Rate of Success of BAX 855 for Treatment of Breakthrough Bleeding Episodes

Success will be defined as a rating of excellent or good using the efficacy rating scale 24 hours after initiation of BAX 855 treatment for the bleeding episode.

Success proportion (95% CI) will be estimated within a general estimating equation (GEE) model framework pooled. The model will account for the fixed effects, bleeding episode severity, age at baseline as a continuous covariate, and the random subject effect.

For the dependent variable (success: yes/no) a binomial distribution and a log link will be assumed, and for the subject effect (defined by a repeated statement) an independence correlation structure will be used to start the estimation. Estimated model parameter values and CI limits will then be back-transformed to the original scale by exponentiation.

13.4.2.3 Number of BAX 855 Infusions for the Treatment of Bleeding Episodes

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

13.4.2.4 Time Intervals Between Bleeding Episodes

The average time interval between 2 consecutive bleeding episodes will be computed for each subject. If a subject does not have any bleeding episode then the observation will be censored at the end of the follow-up time of the respective subject. The median (95% CI) of those average time intervals between 2 bleeding episodes will be estimated.

13.4.2.5 Weight-Adjusted Consumption of BAX 855

Weight-adjusted consumption of BAX 855 for prophylaxis, treating bleeding episodes 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. Only the bleeding episodes consumption with BAX 855 will be summarized.

13.4.3 Patient Reported Outcomes

13.4.3.1 Haemo-SYM

Higher scores on the Haemo-SYM indicate worse symptom severity. Changes from baseline to end of treatment in the Haemo-SYM scores will be tested for statistical significance using a Wilcoxon test for paired samples. Improvement in the Haemo-SYM pain subscale of at least 11 points decreasing will be considered a meaningful improvement (a 1 point change on each pain question). Number and proportion of subjects with meaningful improvement in the Haemo-SYM pain subscale will be tabulated.

13.4.3.2 SF-36

Lower scores on SF-36 indicate worse HRQoL. Changes from baseline to end of treatment in the SF-36 scores will be tested for statistical significance, using a Wilcoxon test for paired samples. Improvement in the SF-36 scale of at least 3 points increasing will be considered a meaningful improvement. Number and proportion of subjects with meaningful improvement in the SF-36 will be tabulated.

13.4.4 Safety Analysis

Frequency counts and percentages will be calculated for SAEs, occurrence of inhibitory and binding 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 clinical laboratory parameters at the start of prophylaxis visit, the follow-up visits, and the end of study visit will be descriptively summarized.

13.4.5 Exploratory Outcome Measures

The exploratory outcome measures will be descriptively summarized and listed.

13.5 Planned Interim Safety Review of the Study

Two (2) interim safety reviews are planned for this study. The results of the safety reviews will not impact the study design and sample size.

An additional safety review is planned upon completion of the phase 2/3 pivotal study.

13.5.1 Interim Safety Review 1

This interim safety review will be conducted when 35 subjects complete 6 months BAX 855 treatment at 30 to 80 IU/kg q5d.

Descriptive statistics of ABR of this period will be provided, in addition, the number and percentage (95% CI) of subjects with ABR = 0 in this 6 months observed period will be provided.

13.5.2 Interim Safety Review 2

This interim safety review will be performed when 20 subjects complete 6 months of BAX 855 treatment at 30 to 80 IU/kg q7d.

The analysis of this interim will be the same as for the first interim safety review.

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 Investigator Report and 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 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 (Baxter) 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 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 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 or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients 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 will be updated, if necessary. This new information and/or revised informed consent form, that have been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study (see Section 16.3).

16.4 Data Monitoring Committee

This study will not require a Data Monitoring Committee (DMC) for routine or ad hoc safety reviews.

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" (Section 8.7), 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, CRFs, 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 CRFs. CRFs will be provided in electronic form.

If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit, the data will be recorded on paper, and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs 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 Schedule of Study Procedures and Assessments

Procedures/Assessments	Screening Visit[a]	Study Visits		End of Study Visit[b] (28 d ± 2 Wks After Last Dose)
		Start of Prophylaxis (Up to 7 d Prior to First Prophylaxis)	Follow-Up (6 Wks [- 1 or + 2 Wks]) & Every 3 Mo [± 4 Wks])	
Informed Consent[c]	X			
Eligibility Criteria	X			
Medical History[d]	X			
Medication History[e]	X			
Concomitant Medications[f]	X	X	X	X
Non-drug Therapies	X	X	X	X
Physical Exam[g]	X	X	X	X
Adverse Events	X[h]	X	X	X
Laboratories[i]	X	X	X	X
Vital Signs[j]	X	X	X	X
Bleeding episodes and their Treatment[k]	X	X	X	X
PROs[l]		X		X
Patient e-diary[m]	X	X	X	X
IP Treatment		X	X	
ABR Estimation[n]			X	

[a] The screening visit procedures, including laboratory evaluations, are to be completed within 45 days prior to the first infusion of BAX 855. Screening procedures for BAX naïve subjects include: confirmation of diagnosis & severity; family history of hemophilia; documentation of a mutation, if known; presence of any target joints; all FVIII replacement therapies used within the last year (see Section 10.3.1 for additional details).

[b] Includes for cases of withdrawal or discontinuation.

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[c] Occurs at enrollment (prior to any study-specific procedure).
[d] Medical history to include hemophilia history.
[e] Medication history to include documentation of all FVIII replacement therapies used within the last year.
[f] Concomitant medications in the last 30 days and any prior history of use of any PEGylated medication (eg, PEG-interferon) at any time in the past.
[g] Physical exam to include a measurement of height (cm) (for subjects less than 18 years of age at enrollment) and weight (kg).
[h] For subjects transitioning from a prior BAX 855 study into this continuation study.
[i] For laboratory assessments, see Section 20.2.
[j] Vital signs to include body temperature (ºC), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg).
[k] Indicates that adverse events, medications, non-drug therapies, and bleeding episodes and their treatment will be continuously monitored and specifically measured at these times.
[l] PROs to include the following depending on patient age: bleed and pain severity using Haemo-SYM (age 18 and older), health-related quality of life using SF-36 (≥ 14 years of age), patient satisfaction with treatment using the Satisfaction Questionnaire, and Patient Activity Level.
[m] E-diaries are to include patient documentation of bleeds, treatment administered and response to BAX 855, and other data as detailed in Section 10.5.
[n] At each consecutive 6 months visit.

20.2 Clinical Laboratory Assessments

Assessments	Screening Visit	Study Visits		End of Study Visit[a] (28 d ± 2 Wks After Last Dose)
		Start of Prophylaxis (Up to 7 d Prior to First Prophylaxis)	Follow-Up (6 Wks [- 1 or + 2 Wks] & Every 3 Mo [± 4 Wks])	
Hematology				
Hemoglobin	W	W	W	W
Hematocrit	W	W	W	W
Red blood cell count	W	W	W	W
White blood cell count with differential[b]	W	W	W	W
Mean corpuscular volume (MCV)	W	W	W	W
Mean corpuscular hemoglobin concentration (MCHC)	W	W	W	W
Platelet count	W	W	W	W
CD4 count	W			
Clinical Chemistry				
Sodium	S	S	S	S
Potassium	S	S	S	S
Chloride	S	S	S	S
Bicarbonate	S	S	S	S
Total protein	S	S	S	S
Albumin	S	S	S	S
Alanine aminotransferase (ALT)	S	S	S	S
Aspartate aminotransferase (AST)	S	S	S	S
Total bilirubin	S	S	S	S
Alkaline phosphatase	S	S	S	S
Blood urea nitrogen (BUN)	S	S	S	S
Creatinine	S	S	S	S
Glucose	S	S	S	S
Lipid panel[c]	S	S	S	S
Viral serology[d]				
HIV-1Ab	S			

Assessments	Screening Visit	Study Visits		End of Study Visit[a] (28 d ± 2 Wks After Last Dose)
		Start of Prophylaxis (Up to 7 d Prior to First Prophylaxis)	Follow-Up (6 Wks [- 1 or + 2 Wks] & Every 3 Mo [± 4 Wks])	
HIV-2 Ab	S			
HBcAb	S			
HBsAb	S			
HBsAg	S			
HCVAb	S			
Specialty Tests				
Blood type[e]	W			
FVIII Tests				
1-stage clotting FVIII activity	P	P	P	P
FVIII chromogenic activity	P	P	P	P
FVIII antigen	P	P	P	P
Immunogenicity Assays[f]				
Inhibitory Abs to FVIII	P	P	P	P
Binding Abs to FVIII, BAX 855 and PEG	P	P	P	P
Anti-CHO Abs	P	P	P	P

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

[a] Includes for cases of withdrawal or discontinuation.

[b] White blood cell count to include basophils, eosinophils, lymphocytes, monocytes, and neutrophils.

[c] Lipid panel to include cholesterol, VLDL, LDL, HDL, and triglycerides.

[d] For viral serology, any positive viral antibody test will be repeated using a new blood sample. Any HCV positive sample will be tested by PCR for viral titer.

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

[f] For binding antibodies, both IgG and IgM antibodies will be measured. A 72-hour washout period is required.

20.3 Karnofsky Score

Karnofsky Score for Performance Status	
Score	**Definition**
100	Normal, no complaints; no evidence of disease
90	Able to perform normal activity; minor signs or symptoms of disease
80	Able to perform normal activity with effort; some signs or symptoms of disease
70	Cares for self, unable to perform normal activity or to do active work
60	Requires occasional assistance but is able to care for most of own needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated, although death not imminent
20	Very sick; hospitalization necessary; active supportive treatment required
10	Moribund; Fatal processes progressing rapidly
0	Dead

Source: Karnofsky et al.[9]

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22. SUMMARY OF CHANGES

Protocol 261302: **Amendment 1 2013 OCT 02**

Replaces: Original: 2013 JUN 18

In this section, changes from the previous version of the Original Protocol, dated 2013 JUN 18, are described and their rationale is given.

1. Throughout the document
   Description of Change: Minor grammatical and/or administrative changes have been made.
   Purpose for the Change: To improve the readability and/or clarity of the protocol.

2. Study Synopsis, 7.2 Primary Objectives, and 8.4.1 Primary Outcome Measures
   Description of Change: "neutralizing FVIII inhibitors" were reworded as "inhibitory antibodies to FVIII".
   Purpose for the Change: To align with other sections of the protocol, the pivotal and surgery studies.

3. Study Synopsis, Sections 9.1 Inclusion Criteria and 9.2 Exclusion Criteria
   Description of Change: Inclusion/Exclusion criteria are applied to all study subjects.
   Purpose for the Change: Clarification and to align with the pivotal and surgery studies.

4. Synopsis, Sections 10.3 Screening and Study Visits, 10.3.3 Follow-up Visits 20.1 Schedule of Study Procedures and Assessments and 20.2 Clinical Laboratory Assessments
   Description of Change: A timing of the first Follow-up visit changed from 1 month (± 2 weeks) to 6 weeks (- 1 or + 2 weeks).
   Purpose for the Change: To ensure immunogenicity testing after 10-15 exposure days for BAX 855 naïve subjects.

5. Section 6.1 Description of Investigational Product
   Description of Change: Additional information was added to more completely describe the BAX 855 molecule, the purpose of this study, how the data with BAX 855 be assessed in this study and the dosing rationale in this study.
   Purpose for the Change: To add more clarity and specific information to support the rationale for this study and the study design including dosing rationale.

6. Sections 8.2 Overall Study Design, 8.6.3 Description of Treatment, 9.1 Inclusion Criteria, 9.2 Exclusion Criteria, 10.3.1 Screening Visit and 10.3.2 Start of Prophylaxis Visit
   Description of Change: Additional wording was added to transition of subjects from other BAX 855 studies.
   Purpose for the Change: Clarification and to align with the pivotal and surgery studies.

7. Section 8.2 Overall Study Design, Section 10.3.1 Screening Visit, and Section 10.3.4 End of Study Visit
   Description of Change: A minimal duration of the washout period was changed to 72 hours.
   Purpose for the Change: To align with the pivotal study and to avoid additional risk of bleeding episodes.

8. Section 8.2.1 Treatment for Surgery or Dental Procedures
   Description of Change: The section was added to provide clarity how subjects will be transferred to and from the surgery study (261204), what factor will be used, what and where to clinical data will be recorded.
   Purpose for the Change: Clarification and to align with the surgery study.

9. Section 8.4.1 Primary Outcome Measures, Section 10.3.1. Screening Visit, Section 10.3.2 Start of Prophylaxis Visit, Section 10.3.3 Follow-up Visits, Section 10.3.4 End of Study, Section 12.14.4 Immunogenicity Assessments, and Section 20.3 Clinical Laboratory Assessments
   Description of Change: A requirement for a 72-hour washout period before immunogenicity tests was added.
   Purpose for the Change: To implement the laboratory requirements and to avoid false results.

10. Section 8.6.3.2 Immune Induction for Inhibitor Development, Section 9.3 Withdrawal and Discontinuation, and Section 12.2 Serious Adverse Events
    Description of Change: The level of detectable FVIII inhibitory antibodies determined by the central laboratory was changed to 0.4 BU.
    Purpose for the Change: The central laboratory was validated for this value.

11. Section 10.3.1 Screening Visit
    Description of Change: Additional wording was added to clarify the assessment for the subjects transitioning from other BAX 855 studies.
    Purpose for the Change: Clarification and to align with the pivotal and surgery studies.

12. Section 10.5 Subject Diary
    Description of Change: Additional wording was added to clarify the section.
    Purpose for the Change: Clarification and to align with the pivotal and surgery studies.

13. Section 12.9 Untoward Medical Occurrences and 12.11 Assessment of Adverse Events
    Description of Change: Description of non-serious events was moved from Section 12.9 to Section 12.11.
    Purpose for the Change: Clarification and to align with the pivotal and surgery studies.

14. Section 12.11 Assessment of Adverse Events
    Description of Change: Additional wording was added to clarify severity rating for adverse events will be recorded for subjects transitioned from other BAX 855 studies.
    Purpose for the Change: Clarification and to align with the pivotal and surgery studies.

15. Section 12.14.7 Biobanking
    Description of Change: Additional wording was added to clarify biobanking.
    Purpose for the Change: Clarification.

16. Section 13.5 Planned Interim Analysis of the Study
    Description of Change: A safety review was added.
    Purpose for the Change: To ensure safety and to be able to provide safety review data upon completion of the pivotal study.

INVESTIGATOR ACKNOWLEDGEMENT

Product: PEGylated rFVIII (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

Phase 3b Continuation Study of the Safety and Efficacy of Prophylactic BAX 855 in PTPs with Severe Hemophilia A

PROTOCOL IDENTIFIER: 261302

CLINICAL TRIAL PHASE: Phase 3B

AMENDMENT 1: 2013 OCT 02

Replaces: Original 2013 JUN 18

OTHER PROTOCOL ID(s)

NCT Number: NCT01945593
EudraCT Number: 2013-002236-24
IND NUMBER: 15299

By signing below, the investigator acknowledges that he/she has read and understands this protocol, 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 Coordinating Investigator Date

Print Name and Title of Coordinating Investigator