CLINICAL STUDY PROTOCOL

PRODUCT: BAX 855 – Pegylated full-length recombinant factor VIII

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

STUDY SHORT TITLE: BAX 855 PK-guided Dosing

PROTOCOL IDENTIFIER: 261303

CLINICAL TRIAL PHASE 3

AMENDMENT 5: 2016 OCT 18

Replaces: AMENDMENT 3: 2015 SEP 04

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Study Sponsor(s):

Baxalta US Inc.
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1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

PPD , MD
PPD
Global Clinical Development Operations
Baxalta Innovations GmbH / Baxalta US Inc.

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g., 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 sponsor and/or ECs, as applicable.

ALL SAEs, INCLUDING SUSARs, ARE TO BE REPORTED ON THE ADVERSE EVENT ELECTRONIC CASE REPORT FORM (eCRF) WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT. IF THE eCRF IS NOT AVAILABLE THEN THE SAE MUST BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR TO MEET THE 24 HOUR TIMELINE REQUIREMENT.

Drug Safety contact information: see SAE Report Form
Refer to SAE Protocol Sections and the study team roster for further information.

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

- AE, Section 13.2
- SAE, Section 13.2.1.1
- SUSARs, Section 13.2.1.2
- Assessment of AEs, Section 13.2.4

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	BAX 855
Name(s) of Active Ingredient(s)	Pegylated full-length Recombinant Factor VIII
CLINICAL CONDITION(S)/INDICATION(S) • Treatment and prophylaxis of bleeding in severe Hemophilia A	
PROTOCOL ID	261303
PROTOCOL TITLE	Phase 3, prospective, randomized, multi-center clinical study comparing the safety and efficacy of BAX 855 following PK-guided prophylaxis targeting two different FVIII trough levels in subjects with severe Hemophilia A
Short Title	BAX 855 PK-guided Dosing
STUDY PHASE	Ph3
PLANNED STUDY PERIOD	
Initiation	First subject in: Q4 2015
Primary Completion	Q2 2018
Study Completion	Q4 2018
Duration	3 years
STUDY OBJECTIVES AND PURPOSE	
Study Purpose 1. To compare the efficacy and safety of pharmacokinetic (PK)-guided treatment with BAX 855 targeting FVIII trough levels of 1-3% and approximately 10% (8-12%) 2. To further characterize PK and pharmacodynamic (PD) parameters of BAX 855	
Primary Objective 1. The primary objective is to compare 2 prophylactic dosing regimens of BAX 855 targeting 2 different FVIII trough levels, by comparing the proportions of subjects achieving a total annualized bleeding rate (ABR) of 0 in the second 6-month study period	
Secondary Objectives Efficacy: • To compare the 2 prophylactic dosing regimens of BAX 855 targeting 2 different FVIII trough levels with respect to the following: ➢ The proportion of subjects in each prophylactic dosing arm achieving a spontaneous ABR and spontaneous[i] joint bleeding rate (AJBR) of 0 in the second 6-month study period ➢ The proportion of subjects in each prophylactic dosing arm with a total, spontaneous ABR and AJBR <2	

[i] i.e., not trauma related.

- The total, spontaneous, and trauma-related ABRs in the 12-month study period
- The reduction in ABR between the 2 treatment arms and the historical ABR prior to study enrollment
- The total weight-adjusted consumption of BAX 855 for each prophylactic regimen
- The joint status using the Hemophilia Joint Health Score (HJHS) and over time
- Health-related quality of life (HRQoL) and pharmacoeconomic outcomes (including Short form-36 questionnaire [SF-36], EuroQol-5 dimension [EQ-5D], Haemo-SYM, and healthcare resource utilization)

- To determine the hemostatic efficacy of BAX 855 in the control of bleeding episodes
- To evaluate the efficacy of BAX 855 for perioperative management, if surgery is required

Safety:

- To determine the immunogenicity of BAX 855
- To determine the safety of BAX 855

Pharmacokinetics:

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

Patient Reported Outcomes

- To assess the difference in the SF-36 physical domain and component change scores from baseline to follow-up between subjects in the 10% trough arm and subjects in the 1-3% trough arm
- To assess the difference in the change of days of physical activity participation from baseline to follow-up between subjects in the 10% trough arm and subjects in the 1-3% trough arm

Exploratory Objectives:

- To determine the potential correlation between thrombin generation assay (TGA) parameters, FVIII trough levels and ABR
- To assess the change in bleed and pain severity scores as measured by the Haemo-SYM questionnaire
- To assess the change in HRQoL using EQ-5D and mental domain and component score of the SF-36
- To assess the difference in the change in healthcare resource utilization from baseline to follow-up between subjects in the 10% trough arm and subjects in the 1-3% trough arm

STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy, Pharmacokinetic, Safety including Immunogenicity, and Pharmacodynamic
Control Type	Dose-Response
Study Indication Type	Prevention, Treatment
Intervention Model	Parallel design
Blinding/Masking	Open label

Study Design	This study is a Phase 3, prospective, randomized, open-label, multicenter study to compare the safety and efficacy of a PK-guided BAX 855 treatment regimen targeting 2 different FVIII trough levels in approximately 116 subjects with severe hemophilia A to have 96 subjects evaluable (48 per treatment arm).
Planned Duration of Subject Participation	The subject's participation will last approximately 15-16 months and is based on the assumption that completion of screening procedures will require approximately 6 weeks; PK assessments, dose calculation and randomization will take 6-8 weeks and the treatment period from the baseline visit to study completion will be 12 months.

Primary Outcome Measure

1. Presence or absence of any bleedings in the second 6-month study period

Secondary Outcome Measures

Efficacy

1. Total, spontaneous, and traumatic ABR, and spontaneous AJBR
2. Total weight-adjusted consumption of BAX 855
3. Overall hemostatic efficacy rating at 8 (±1) hours after the initiation of treatment and at resolution of bleed
4. Number of BAX 855 infusions needed for the treatment of bleeding episodes
5. HJHS
6. Intra-, post- and perioperative hemostatic efficacy in case of surgery
7. Intra- and postoperative blood loss in case of surgery

Safety

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

Patient Reported Outcomes (PROs)

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

Pharmacokinetics

1. BAX 855 PK parameters based on FVIII activity at baseline and steady state, if applicable:
   a. AUC0-∞ (area under the plasma concentration versus time curve from time 0 to infinity), IR at 15-30 minutes post-infusion, $T_{1/2}$ (plasma half-life), MRT (mean residence time), CL (clearance), maximum plasma concentration (Cmax) and time to maximum concentration in plasma (Tmax), Vss (Volume of distribution at steady state)
   b. IR over time

Exploratory Outcome Measures

1. Thrombin generation assay (TGA) parameters (lag time, time to peak thrombin generation, peak thrombin generation, and endogenous thrombin potential [ETP])
2. Bleed and pain severity scores as measured by the Haemo-SYM questionnaire
3. HRQoL as assessed using EQ-5D and mental domain and component scores of the SF-36
4. Healthcare resource utilization

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**BAX 855** **Dosage form**: injection, powder, lyophilized, for solution **Dose and Dosage frequency**: BAX 855 dose will be PK-guided to maintain FVIII target trough levels of 1-3% or approximately 10% (8-12%) at the following dosing frequencies: FVIII trough levels of 1-3%: approximately twice weekly[ii] FVIII trough levels of approximately 10% (8-12%): every other day[iii] **Mode of Administration**: intravenous bolus
SUBJECT SELECTION	
Targeted Accrual	Approximately 116 subjects will be enrolled to have 96 subjects evaluable (48 in each prophylaxis dosing arm).
Number of Groups/ Arms/Cohorts	2

Inclusion Criteria for Subjects Transitioning from Another BAX 855 study:

1. Subject has completed the end of study visit of a BAX 855 study or is transitioning from the ongoing Continuation Study 261302
2. Subject is either receiving on-demand or prophylactic treatment with BAX 855 and had an ABR of ≥2 documented and treated during the past 12 months
3. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥200 cells/mm^3, as confirmed by central laboratory
4. Subject is willing and able to comply with the requirements of the protocol

Inclusion Criteria for Newly Recruited Subjects:

1. Subject is 12 to 65 years old at the time of screening
2. Subject has severe hemophilia A (FVIII clotting activity <1%) as confirmed by central laboratory OR by historically documented FVIII clotting activity performed by a certified clinical laboratory, optionally supported by a FVIII gene mutation consistent with severe hemophilia A
3. Subject has been previously treated with plasma-derived FVIII concentrates or recombinant FVIII for ≥150 documented EDs

[ii] Twice weekly: infusion on day 3 or 4, at 2 different doses to cover the different treatment intervals, or every 3.5 days. According to individual PK, frequency may be adjusted based on FVIII trough levels.
[iii] Depending on subject's individual PK, frequency may be adjusted.

4. Subject is either receiving on-demand treatment or prophylactic treatment and had an annual bleeding rate of ≥2 documented and treated during the past 12 months
5. Subject has a Karnofsky performance score of ≥60 at screening
6. Subject is HIV-; or HIV+ with stable disease and CD4+ count ≥200 cells/mm^3, as confirmed by central laboratory at screening
7. Subject is hepatitis C virus negative (HCV-) by antibody (if positive, additional PCR testing will be performed), as confirmed by central laboratory at screening; or HCV+ with chronic stable hepatitis
8. If female of childbearing potential, subject presents with a negative urine pregnancy test and agrees to employ adequate birth control measures for the duration of the study
9. Subject is willing and able to comply with the requirements of the protocol

Exclusion Criteria

Exclusion Criteria for Subjects Transitioning from Another BAX 855 study:

1. Subject has developed a confirmed inhibitory antibody to FVIII with a titer of ≥0.6 Bethesda Units (BU) using the Nijmegen modification of the Bethesda assay as determined at the central laboratory during the course of the previous BAX 855 study
2. Subject has been diagnosed with an acquired hemostatic defect other than hemophilia A
3. The subject's weight is <35 kg or >100 kg
4. Subject's platelet count is <100,000/mL
5. Subject has an abnormal renal function (serum creatinine >1.5 times the upper limit of normal)
6. Subject has active hepatic disease with alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels ≥5 times the upper limit of normal
7. Subject is scheduled to receive a systemic immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day, or α-interferon) other than anti-retroviral chemotherapy during the study
8. Subject has a clinically significant medical, psychiatric, or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject's safety or compliance
9. Subject is planning to take part in any other clinical study during the course of the study
10. Subject is a member of the team conducting this study or is in a dependent relationship with one of the study team members. Dependent relationships include close relatives (i.e., children, partner/spouse, siblings, parents) as well as employees of the investigator or site personnel conducting the study

Exclusion Criteria for Newly Recruited Subjects

1. Subject has detectable FVIII inhibitory antibodies (≥0.6 BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening
2. Subject has a history of confirmed FVIII inhibitors with a titer ≥0.6 BU (as determined by the Nijmegen modification of the Bethesda assay or the assay employed with the respective cut-off in the local laboratory) at any time prior to screening
3. Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (e.g., qualitative platelet defect or von Willebrand's disease)

4. The subject's weight is <35 kg or >100 kg
5. Subject's platelet count is <100,000/mL
6. Subject has known hypersensitivity towards mouse or hamster proteins, PEG or Tween 80
7. Subject has severe chronic hepatic dysfunction (e.g., ≥5 times upper limit of normal ALT and/ or AST, as confirmed by central laboratory at screening, or a documented INR >1.5)
8. Subject has severe renal impairment (serum creatinine >1.5 times the upper limit of normal)
9. Subject has current or recent (<30 days) use of other pegylated drugs prior to study participation or is scheduled to use such drugs during study participation
10. Subject is scheduled to receive during the course of the study, a systemic immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day, or α-interferon) other than anti-retroviral chemotherapy
11. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
12. Subject has a medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance
13. Subject is a member of the team conducting this study or is in a dependent relationship with one of the study team members. Dependent relationships include close relatives (i.e., children, partner/spouse, siblings, parents) as well as employees of the investigator or site personnel conducting the study.

STATISTICAL ANALYSIS

Sample Size Calculation

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

Under these assumptions 48 subjects per study group are needed to reject the null hypothesis of no difference between the study arms against a 2-sided alternative at the 5% level of statistical significance with 80% power. Assuming a drop-out rate of close to 10%, and 10-15% of subjects being non-compliant, approximately 116 subjects are planned to be randomized between the 2 BAX 855 regimens with an allocation ratio of 1:1.

Planned Statistical Analysis

The proportion of subjects with ABR = 0 in the 2 prophylaxis treatment regimens in the second 6 months period will be compared using a chi-square test with continuity correction at a 2-sided 5% level of significance. For all outcome measures, bleeding rates will be analyzed using a negative binomial model and descriptive statistics will be presented for the 2 dosing regimens for other outcomes. Point estimates (mean or median) and 95% confidence intervals will be computed if feasible.

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Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	annualized bleeding rate
AE	adverse event
AJBR	annualized joint bleeding rate
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 Baxalta's pegylated recombinant FVIII (rFVIII)
BU	Bethesda unit
(US) CFR	(US) Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
CL	total body clearance
Cmax	maximum plasma concentration
(e)CRF	(electronic) case report form
CTA	Clinical Trial Agreement
DI	dose intensification
DMC	data monitoring committee
EC	ethics committee
eCRF	electronic Case Report Form
ED	exposure day
EDC	Electronic Data Capture
ELISA	enzyme-linked immunoabsorbent assay
EMA	European Medicines Agency
EQ-5D	EuroQol-5 dimension
ETP	endogenous thrombin potential
FVIII	factor VIII
GCP	Good Clinical Practice
GEE	general estimating equation

Abbreviation	Definition
GLM	general linear model
h	hour(s)
HAV	hepatitis A virus
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HJHS	hemophilia joint health score
HRQoL	health-related quality of life
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
INR	international normalized ratio
IP	investigational product
IR	incremental recovery
ITI	immune tolerance induction
IU	international unit (s)
i.v.	intravenous(ly)
LDL	low density lipoprotein
MRI	magnetic resonance imaging
MRT	mean residence time

Abbreviation	Definition
NMC	non-medical complaint
PCR	polymerase chain reaction
PD	pharmacodynamic
pdFVIII	plasma-derived factor VIII
PEG	polyethylene glycol
PK	pharmacokinetic(s)
PP	per protocol
PRO	patient reported outcomes
PTP	previously treated patient
rFVIII	recombinant factor VIII
SAE	serious adverse event
SAER	serious adverse event report
SAS	Safety Analysis Set
SF-36	Short form-36 questionnaire
SIC	subject identification code
SUSAR	suspected unexpected serious adverse reaction
SWFI	sterile water for injection
$T_{1/2}$	plasma half-life
TGA	thrombin generation assay
Tmax	time to maximum concentration in plasma
US	United States
VLDL	very low density lipoprotein
Vss	volume of distribution at steady state
VWF	von Willebrand factor

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

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

Since the half-life of current FVIII products is in the range of 10-14 hours [1,2], current prophylaxis regimens call for infusion of FVIII every other day or every 2-3 days when based on each patient's individual PK profile.[3] Pegylation of FVIII is designed to prolong the half-life of FVIII, with the intent of reducing the frequency of administration while maintaining similar therapeutic benefit as existing FVIII products; improving patient convenience and compliance with therapy; and thereby improving overall health outcomes. Prolongation of half-life of FVIII may also increase efficacy by increasing the FVIII trough levels while maintaining the frequency of administration of existing FVIII concentrates every other day.

BAX 855 consists of rFVIII protein molecules with covalently bound PEG chains linked to the protein using a stable linker. The product is reconstituted with sterile water for injection (SWFI) and is administered intravenously (i.v.) as a solution by bolus infusion. It uses the same stabilizing agents (mannitol, trehalose, histidine and glutathione) as the rFVIII product (octocog alfa, ADVATE) from which it is derived. Comprehensive preclinical studies as well as 2 successfully completed studies (Baxter clinical study 261101 and 261201) 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's Brochure (IB).

No comparator drug product will be used in this study for prophylaxis or treatment of bleeding. Treatment regimens are based on individual PK parameters and FVIII trough levels with a target trough level of 1-3% given twice weekly, or approximately 10% (8-12%) FVIII given every other day.

6.2 Clinical Condition/Indication

Hemophilia A is an X-chromosome-linked recessive, congenital bleeding disorder caused by deficient or defective coagulation due to deficiency of FVIII. The absence of FVIII leads to 'spontaneous' bleeding episodes (occurring primarily in joints, muscles, and less commonly, in soft tissues) and to excessive bleeding following trauma or injury. Hemophilia A is currently treated with FVIII replacement using either plasma-derived (pdFVIII) or rFVIII concentrates.[4,5]

The intended indication for BAX 855 is treatment and prophylaxis of bleeding and perioperative management in subjects with hemophilia A. The clinical program of BAX 855 is in compliance with the EMA/CHMP/BPWP/144533/2009 guidelines for FVIII in hemophilia A.[6]

The major objective of a prophylactic treatment in severe hemophilia A patients is to prevent bleeding episodes, in particular frequent joint bleeding. Bleeding episodes in a joint cause detrimental changes in synovial tissue and cartilage, which trigger synovial cell inflammation and proliferation, cartilage damage and bone erosion.[7] Intra-articular bleeding is the most important risk factor and seems to play a key role not only for the inflammation but also for the direct destructive process in the joint.[8] A number of prospective and retrospective clinical studies have demonstrated that prophylactic treatment reduced the number of break-through bleeds compared to on-demand treatment.[9,10,11,12,13,14,15,16,17,18]

Current management of severe hemophilia A includes on-demand treatment for bleeding episodes and prophylaxis to prevent bleeds.[19] A prospective clinical study using individually pharmacokinetic (PK) adjusted prophylaxis dosing targeting a FVIII trough level of 1% can reduce the annualized bleed rate (ABR) from 44 during on demand treatment to 1 during standard prophylaxis. The optimal prophylaxis regimen is still under scientific discussion but the frequency of break through bleedings during prophylactic treatment is assumed to depend on the time spent with a low FVIII level. Thus, dose recommendations used in prophylaxis are designed to keep the FVIII trough level above 1% of the normal level.[19]

However, the 1% level is not applicable to prevent bleeding episodes in all patients. Especially patients with damaged joints often bleed in spite of maintenance of a 1% trough level, although this association is difficult to access in clinical practice.[20] A pioneering bench mark study by Den Uijl et al. has suggested that the annual number of bleeds is approaching zero when baseline levels of FVIII ≥10% are maintained.[21]

Although there are no established criteria for determining how many joint bleeds can be tolerated before irreversible damage occurs, some studies reported that more than 2-5 joint bleeds in total lead to impaired joint scores [22,23,24] whereas annual bleed rates between 0.1 and 2.7 did not lead to joint damage.[25,26,27]

In an advanced stage these events accumulate and result in permanent loss of joint mobility leading to crippling arthropathy, the hallmark of advanced severe hemophilia A. For the assessment of joint impairment, joint scores have been developed. One of the best established scores is the Hemophilia Joint Health Score (HJHS). The HJHS is a validated 11-item scoring tool based on radiologic and clinical evaluation, sensitive to detect early signs and minor changes.[28]

6.3 Population to be Studied

Adolescent and adult subjects (aged 12-65 years) with severe hemophilia A (FVIII <1%), of all races and ethnic groups, without history of or currently confirmed FVIII inhibitors (≥0.6 Bethesda Units [BU]) will be studied. All subjects will have been previously treated with pdFVIII or rFVIII concentrates with ≥150 documented exposure days (EDs) (previously treated patients; PTP). Subjects receiving prophylaxis and on-demand treatment will be included in this study and they must have had at least 2 documented and treated bleeds within the 12 months prior to enrolment.

Justification for enrollment of adolescent 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. Adolescent subjects, in particular if they are physically active, are expected to benefit from a new treatment approach with target FVIII trough levels of approximately 10% using a new recombinant full-length rFVIII molecule with an extended half-life. Moreover, results from nonclinical repeated toxicology studies, the core safety pharmacology package and the completed clinical Phase 1, Phase 2/3 pivotal, Phase 3 pediatric studies, as well as the ongoing Phase 3 continuation and surgery studies have not raised any safety or tolerability concerns. Furthermore, the parent protein molecule ADVATE has been used extensively in the entire pediatric population with no unforeseen adverse events (AEs).

6.4 Findings from Nonclinical and Clinical Studies

6.4.1 Findings from Nonclinical Studies

BAX 855 is manufactured by covalently binding a branched PEG reagent with a molecular weight of 20 kDA to Baxalta's rFVIII (octocog alfa, ADVATE). Baxalta's octocog alfa is expressed in Chinese hamster ovary (CHO) cells by a plasma/albumin free cell culture method and is the active substance in Baxalta's licensed product ADVATE. Thus, the viral safety of BAX 855 is ensured by the octocog alfa (ADVATE) bulk drug substance manufacturing process as any potential risk of contamination with viruses or adventitious agents during the subsequent manufacturing steps of BAX 855 has been minimized. No substances of animal or human origin are added throughout the entire manufacturing process of BAX 855.

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

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

6.4.2 Findings from Clinical Studies

To date, 3 clinical studies have been completed:

- Study 261101 is a first in human study to assess the safety and PK of BAX 855 in PTPs aged 18-65 years with severe hemophilia A with ≥150 EDs to FVIII products, conducted in Europe and Japan. A total of 24 subjects were enrolled; 19 were treated and 18 were evaluable for PK analysis. Nine were treated with 30 IU/kg (Cohort 1) and 10 were treated with 60 IU/kg (Cohort 2) of BAX 855, including 2 subjects from Japan. BAX 855 appeared to be safe and well tolerated after a single dose administration and no subject developed inhibitors to FVIII or binding antibodies to PEG. The mean plasma half-life ($T_{1/2}$) was 1.4- and 1.5-fold higher for BAX 855 compared to ADVATE in Cohorts 1 and 2, respectively, demonstrating prolonged circulation of BAX 855 compared to ADVATE. These data support the use of the BAX 855 dosing regimens planned in this study.

- Study 261201 is a Phase 2/3 study in which BAX 855 was found to be safe and well tolerated in all 137 treated subjects. None of the subjects developed inhibitory antibodies to FVIII of ≥0.6 BU/mL or persistent binding antibodies to FVIII, PEG-FVIII, PEG, or CHO proteins. The study confirmed the results of the Phase 1 study 261101, demonstrating that BAX 855 extends the mean $T_{1/2}$ by approximately 1.4-fold and MRT by approximately 1.5-fold as compared to ADVATE. Twice weekly prophylactic infusions at the intended dose of 45 ±5 IU/kg BAX 855 resulted in an ABR which was significantly lower than that observed with on-demand treatment with a prophylaxis/on-demand ABR ratio of 0.10. Approximately 40% of subjects treated on prophylaxis did not experience any bleeding episodes, while all subjects treated on-demand experienced bleeding episodes. BAX 855 was efficacious in the treatment of bleeding episodes with 96.1% rated excellent or good and 95.9% treated with 1 or 2 infusions. This study demonstrated that BAX 855 is safe and efficacious in treating bleeding episodes and in prophylaxis administered twice weekly in adults and adolescents ≥12 years with severe hemophilia A.
- Study 261202 is a Phase 3 study in which BAX 855 was found to be safe and well tolerated in all 66 treated pediatric subjects <12 years of age. None of the subjects developed inhibitory antibodies to FVIII ≥0.6 BU or persistent binding antibodies against FVIII, PEG-FVIII, PEG, or CHO proteins which could have been correlated to an impaired hemostatic efficacy or safety profile. The study showed an extended $T_{1/2}$ of BAX 855 also in children (N = 31); $T_{1/2}$ and MRT were 1.3- to 1.5-times longer for BAX 855 than for ADVATE. Twice weekly prophylactic infusions at the intended dose of 50 ±10 IU/kg resulted in a point estimate for the mean ABR of 3.04 (95% CI: 2.208-4.186); the overall median ABR was 2.00 (range: 0, 49.8). The point estimate for spontaneous bleeds was 1.164 (95% CI: 0.740-1.832) with a median annualized spontaneous bleeding rate of 0 (range: 0, 11.5) in all subjects. For joint bleeds, the point estimate for the mean ABR was 1.103 (95% CI: 0.637-1.910). The median joint ABR was 0 (range: 0, 14.3) in all subjects. Overall, 37.9% of subjects did not experience any bleeding episodes, 67.6% of subjects did not have any spontaneous bleeds, and 72.7% of subjects had no joint bleeds. BAX 855 was efficacious in the treatment of bleeding episodes: 90.0% had an efficacy rating of excellent or good and 91.5% were treated with 1 or 2 infusions. Twice-weekly administration of BAX 855 at a dose of 50 ±10 IU/kg was safe and efficacious for prophylaxis and control of bleeding in pediatric subjects <12 years of age with severe hemophilia A.

Three clinical studies are currently ongoing:

- Study 261204 is a Phase 3 study to assess efficacy in subjects undergoing major or minor elective or minor emergency surgical, dental, or other invasive procedures. The dose and frequency of BAX 855 administered is individualized based on the subject's PK parameters (determined from a presurgical assessment) for major surgeries and IR for minor surgeries and the FVIII target levels required for the planned procedure. Based on an interim analysis, perioperative and intraoperative hemostatic efficacy of BAX 855 was rated as "excellent", for 15/15 procedures. The postoperative efficacy of BAX 855 was rated as "excellent" for 13 procedures, "good" for one procedure, and the rating was pending for one procedure at the time of data cut-off. These results of 11 major and 4 minor surgeries in 15 hemophilia A subjects indicate that BAX 855 has excellent efficacy for perioperative use in major surgery with blood loss comparable to that expected for the same type of procedure performed in a non-hemophilic subject.
- Study 261302 is a Phase 3b continuation study evaluating safety and efficacy in the prophylaxis of bleeding in subjects who have completed previous BAX 855 studies. This study also explores different treatment regimens. After closure of enrollment for pediatric study 261202 and pivotal study 261201, the continuation study is open also to BAX 855 naïve pediatric subjects.
- Study 261203 is a Phase 3, prospective, open-label, multicenter study to assess the safety, immunogenicity and hemostatic efficacy of BAX 855 in previously untreated patients <6 years of age with severe hemophilia A (baseline FVIII level <1%) and <3 EDs to ADVATE, BAX 855, or fresh frozen plasma in at least 100 evaluable subjects. The subject's participation will last approximately 2 years, depending on the type of treatment, and up to 5.5 years in total, in case of inhibitors.

The results to date demonstrate that BAX 855 is safe and efficacious in treating bleeding episodes and in prophylaxis, including long-term prophylaxis, administered twice weekly in children, adults, and adolescents with severe hemophilia A as well as in surgical prophylaxis. In addition, the data consistently demonstrate prolonged circulation of BAX 855 in comparison with the parent molecule ADVATE.

Additional information from clinical studies can be found in the BAX 855 IB.

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

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

Since BAX 855 is a pegylated form of ADVATE, there is also the potential risk of inducing anti-PEG antibodies following BAX 855 administration. Binding antibodies against PEG are present in the healthy population and in subjects with hemophilia A. BAX 855 may react with pre-existing anti-PEG antibodies, potentially resulting in a clinical hypersensitivity reaction or increased clearance of BAX 855 from circulation. BAX 855 and ADVATE showed a similar immunogenicity profile in preclinical in vitro and in vivo studies. Data from preclinical studies indicate that pegylated human FVIII can only induce antibodies against PEG when FVIII is recognized as a foreign protein that can provide immunogenic epitopes for CD4+ T cells.

In the pivotal Phase 2/3 (study 261201) and pediatric Phase 3 (study 261202) studies, it could be demonstrated that the presence of anti-PEG antibodies at screening or transiently occurring in some subjects did not have an impact on hemostatic efficacy or safety and that BAX 855 did not induce persistent antibodies to PEG or BAX 855. For 3 subjects with positive antibody results in pediatric study 261202, based on the current data no conclusion can be drawn whether these antibodies are of transient or persistent nature because immunoglobulin G (IgG) antibodies against PEG-FVIII in 2 subjects were only observed at study completion/termination; 1 subject was positive for antibodies against PEG-FVIII at Week 5, Week 12, and at study completion with antibody titers that did not increase over time. However, there was no impact on safety or hemostatic efficacy.

Previously treated patients with a high degree of previous exposure to FVIII should be immunotolerant to FVIII and are considered to have a low risk of developing antibodies against FVIII. Therefore, the risk for PTPs with severe hemophilia A who do not have neutralizing antibodies against FVIII (inhibitors) are also expected to be at low risk to develop antibodies against BAX 855. Based on an integrated analysis of 3 completed and

2 ongoing studies with 234 unique subjects of whom 186 subjects had ≥50 EDs to BAX 855, 114 ≥100 EDs to BAX 855, and 72 ≥150 EDs to BAX 855, none of them developed inhibitory antibodies to FVIII ≥0.6 BU at any time during the studies. Also, none of these 234 subjects developed persistent binding antibodies to FVIII, PEG-FVIII, or PEG, except 3 pediatric subjects who had antibodies at the time of the data cut-off date where no final conclusion can be drawn yet. However, there was no temporal association with AEs or increased occurrence of spontaneous bleeding episodes. None of the subjects developed antibodies against CHO proteins at any timepoint. Moreover, no immune responses with a clinical impact and no evidence of hypersensitivity reactions in PTPs were observed.

The integrated analysis of safety data demonstrated that BAX 855 was safe and well tolerated in the 234 unique PTPs with severe hemophilia A from the 3 completed and 2 ongoing studies. Subjects were treated with BAX 855 for prophylaxis, bleeding episodes, perioperative management, or received a single-dose for a PK evaluation. One hundred and seventy-four subjects were treated long-term with BAX 855 by initiating treatment in the Phase 1, pivotal, pediatric, or surgery study and continuing in the continuation study. No AEs considered allergic or hypersensitivity reactions were observed in any of the studies with PTPs. The results demonstrate that BAX 855 is safe and efficacious in treating bleeding episodes and in prophylaxis, including long-term prophylaxis, administered twice weekly in children, adults and adolescents with severe hemophilia A. In addition, the data consistently demonstrate prolonged circulation of BAX 855 in comparison with the parent molecule ADVATE. Furthermore, the results of 11 major and 4 minor surgeries in 15 hemophilia A subjects indicate that BAX 855 is efficacious for perioperative use with blood loss comparable to that expected for the same type of procedure performed in a non-hemophilic subject.

The comparability of BAX 855 to ADVATE, the preclinical safety profile of BAX 855, and the available clinical data from the Phase 1, 2/3, and 3 studies, suggest an acceptable risk benefit profile for BAX 855. Additional details related to risks and benefits can be found in the BAX 855 IB.

6.6 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives 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 compare the efficacy and safety of PK-guided treatment with BAX 855 targeting FVIII trough levels of 1-3% and approximately 10% (8-12%).
- To further characterize PK and PD parameters of BAX 855

7.2 Primary Objective

The primary objective of the study is to compare 2 prophylactic dosing regimens of BAX 855 targeting 2 different FVIII trough levels, by comparing the proportions of subjects achieving a total ABR of 0 in the second 6-month study period.

7.3 Secondary Objectives

The secondary objectives are:

7.3.1 Efficacy

1. To compare the 2 prophylactic dosing regimens of BAX 855 targeting 2 different FVIII trough levels with respect to the following:
   - The proportion of subjects in each prophylactic dosing arm achieving a spontaneous[iv] ABR and spontaneous[iv] joint bleeding rate (AJBR) of 0 in the second 6-month study period
   - The proportion of subjects in each prophylactic dosing arm with a total, spontaneous ABR and AJBR <2
   - The total, spontaneous, and trauma-related ABRs in the 12-month study period
   - The reduction in ABR between the 2 treatment arms and the historical ABR prior to study enrollment
   - The total weight-adjusted consumption of BAX 855 for each prophylactic regimen
   - The joint status using the HJHS and over time
   - Health-related quality of life (HRQoL) and pharmacoeconomic outcomes (including Short form-36 questionnaire [SF-36], EuroQol 5 dimension [EQ-5D], Haemo-SYM, and healthcare resource utilization)
2. To determine the hemostatic efficacy of BAX 855 in the control of bleeding episodes

[iv] i.e., not trauma-related

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

7.3.2 Safety

1. To determine the immunogenicity of BAX 855
2. To determine the safety of BAX 855

7.3.3 Pharmacokinetics

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

7.3.4 Patient Reported Outcomes

1. To assess the difference in the SF-36 physical domain and component change scores from baseline to follow-up between subjects in the 10% trough arm and subjects in the 1-3% trough arm
2. To assess the difference in the change of days of physical activity participation from baseline to follow-up between subjects in the 10% trough arm and subjects in the 1-3% trough arm

7.4 Exploratory Objectives

1. To determine the potential correlation between thrombin generation assay (TGA) parameters, FVIII trough levels and ABR
2. To assess the change in bleed and pain severity scores as measured by the Haemo-SYM questionnaire
3. To assess the change in HRQoL using EQ-5D and mental domain and component scores of the SF-36
4. To assess the difference in the change in healthcare resource utilization from baseline to follow-up between subjects in the 10% trough arm and subjects in the 1-3% trough arm

8. STUDY DESIGN

8.1 Brief Summary

This study is a Phase 3, prospective, randomized, open-label, multicenter study to compare the safety and efficacy of a PK-guided BAX 855 treatment regimen targeting 2 different FVIII trough levels of 1-3% and approximately 10% (8-12%) in adolescent and adult PTPs with severe hemophilia A (<1% FVIII). Enrolled subjects will undergo an initial PK assessment following a single administration of BAX 855 to determine the subject's individual PK parameters to tailor the dose for the targeted FVIII trough levels. Subjects will be randomized to one of 2 study arms of 58 subjects each, to target trough FVIII levels of 1-3% or approximately 10% (8-12%), for a treatment period of 12 months. An optional repeat PK at steady state will be performed after 9 months of treatment.

8.2 Overall Study Design

This study is a Phase 3, prospective, randomized, open-label, multicenter study to compare the safety and efficacy of PK and FVIII trough level-guided BAX 855 treatment targeting FVIII trough levels of 1-3% or approximately 10% (8-12%) in a total of 96 evaluable (48 in each of 2 study arms) adolescent and adult PTPs with severe hemophilia A (<1% FVIII). Approximately 116 subjects will be enrolled for a total of 96 evaluable subjects (assuming a dropout rate of close to 10% and 10-15% of subjects being non-compliant). Subjects from the BAX 855 continuation (261302) the BAX 855 surgery (261204) study, the BAX 855 pediatric (261202) study[v], and newly recruited subjects including BAX 855-naïve subjects will participate.

Subjects will be screened per protocol inclusion/exclusion criteria and, following confirmation of eligibility, will undergo an initial PK assessment following a single administration of BAX 855 (60 ±5 IU/kg) to determine PK parameters. Following the PK assessment, subjects will be randomized to one of 2 dosing regimens: the standard treatment arm will target FVIII trough levels of 1-3% and the second, intensified treatment arm will target trough levels of approximately 10% (8-12%) FVIII. The dose and frequency will be based on each subject's individual PK. More frequent dosing should be considered if single doses of >80 IU/kg are required or regular FVIII peak levels of 200% would be reached.

[v] In case subject is at least 12 years of age at the time of informed consent of this study.

Subjects will complete study visits as follows to undergo efficacy, safety, and PRO assessments: Baseline Visit, Visit 1 at 4 weeks ±5 days; Visit 2 at 8 weeks ±1 week; Visit 3 at 3 months ±2 weeks; Visit 4 at 4.5 months ±2 weeks; Visit 5 at 6 months ±1 week (26 ±1 weeks); Visit 6 at 7.5 months ±2 weeks; Visit 7 at 9 months ±2 weeks; Visit 8 at 10.5 months ±2 weeks; and the Study Completion/Termination Visit for follow-up at 12 months ±1 week (53 [±1] weeks). It must be ensured that the second 6-month study period will consist of at least 26 weeks following the 6 month-study visit scheduled at 26 (±1) weeks and that the subject will have received his PK-tailored dosing regimen for at least 52 weeks. The following items are discussed with the subject at each study visit: concomitant medications, non-drug therapies, AEs, bleeding episodes and their treatment, including details of target joint bleedings, as well as any physical activity within 8 h prior to the onset of a bleeding episode, type and duration of physical activity with a risk category of 2.5 or higher [29], or contact sport for a duration of 15 minutes or more, and to review the subject diary. For subjects without bleeding episodes, Visits 6 and 8 are phone visits. If, however, a subject has a bleeding episode, instead of a phone visit the subject must attend a site visit to assess FVIII trough levels and IR and re-evaluate the PK-guided regimen, the subject's physical activity and compliance. In these cases the subject will undergo all planned assessments for a study visit, including assessment of vital signs, physical examination, and all laboratory assessments.

The overall study design is illustrated in Figure 1.

8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 3 years from study initiation (i.e., first subject enrolled) to study completion. The recruitment period is expected to approximately 16 months.

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

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

The primary outcome measure is the presence or absence of any bleedings in the second 6-month study period.

8.4.2 Secondary Outcome Measures

8.4.2.1 Efficacy

1. Total, spontaneous, and traumatic ABR, and spontaneous AJBR
2. Total weight-adjusted consumption of BAX 855
3. Overall hemostatic efficacy rating at 8 (±1) hours after the initiation of treatment and at resolution of bleed.
4. Number of BAX 855 infusions needed for the treatment of bleeding episodes
5. HJHS
6. Intra-, post- and perioperative hemostatic efficacy in case of surgery
7. Intra- and postoperative blood loss in case of surgery

8.4.2.2 Safety

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

8.4.2.3 Patient Reported Outcomes

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

8.4.2.4 Pharmacokinetics

1. BAX 855 PK parameters based on FVIII activity at baseline and steady state, if applicable:
   - AUC0-∞ (area under the plasma concentration versus time curve from time 0 to infinity), IR (incremental recovery) at 15-30 minutes post-infusion, $T_{1/2}$, MRT, CL (clearance), maximum plasma concentration (Cmax) and time to maximum concentration in plasma (Tmax), Vss (Volume of distribution at steady state)
   - Incremental recovery (IR) over time

8.4.3 Exploratory Outcome Measures

1. Thrombin generation assay (TGA) parameters (lag time, time to peak thrombin generation, peak thrombin generation, and endogenous thrombin potential [ETP])
2. Bleed and pain severity scores as measured by the Haemo-SYM questionnaire
3. HRQoL as assessed using EQ-5D and mental domain and component scores of SF-36
4. Health resource utilization

8.5 Randomization and Blinding

This is a randomized, open-label, concurrent, dose regimen comparison clinical study. In order to minimize/avoid bias, once eligibility is confirmed, subjects will be randomly assigned to one of 2 treatment regimens with PK-guided dosing targeting FVIII trough levels of 1-3% or approximately 10% (8-12%) in a 1:1 ratio. Randomization occurs after the PK assessment and will be stratified according to subjects' pre-study treatment regimen/ABR (prophylaxis with ABR <5 vs. prophylaxis with ABR >=5 vs. on-demand).

8.6 Study Stopping Rules

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

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

The study may be terminated, if 1 or more of the following criteria are met:

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

8.7 Investigational Product(s)

8.7.1 Packaging, Labeling, and Storage

BAX 855 is formulated as a sterile, highly purified protein preparation in lyophilized form for i.v. infusion and is provided in single-dose vials with a vial of diluent (2 mL or 5 mL SWFI, as available). A butterfly transfer set with luer-lock syringes and a needleless transfer device (BAXJECT II high-flow [HF] or BAXJECT III, as available) will be used for reconstitution and bolus i.v. delivery. 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 potencies of BAX 855 may be used, depending upon availability: 250, 500, 1,000 and 2,000 IU/vial. Additional potencies of 750 IU/vial, 1500 IU/vial and 3000 IU/vial will be used once available.

The recommended storage conditions for BAX 855 are 2°C to 8°C (36°F to 46°F) and it should not be allowed to freeze. BAX 855 should be stored and protected from light.

The reconstituted product should ideally be used immediately but no longer than 3 hours after reconstitution.

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

8.7.2 Administration

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

BAX 855 dose calculation will be based on the stated actual potency of each vial.

PK assessment and determination of IR

For the PK assessment in individual subjects (initial and at steady state, if applicable), only vials of the same lot with a nominal potency of 500 IU should preferably be used. If due to a subject's weight, the PK or IR infusion volume will exceed 30 mL, 1000 IU vials should preferably be used to reduce the volume administered.

The total calculated dose may be rounded up or down to the nearest whole vial in case 500 IU potency vials are used. However, in case vials with a nominal potency of 1,000 IU/vial are used, the total calculated dose should not be rounded up or down to the nearest whole vial to ensure accurate dosing (e.g., 2.5 vials).

In approximately 30 subjects who have a PK-guided prophylactic dose of ≥40 IU/kg, at least one IR following baseline IR should be determined using vials with a nominal potency of 3000 IU, once available. The total calculated dose should not be rounded up or down to the nearest whole vial to ensure accurate dosing. Only vials of the same lot should be used for one IR infusion.

Infusions for prophylaxis and treatment of bleeding episodes

All available potencies will be used for prophylaxis and treatment of bleeding episodes. Two different lots per infusion may be used, however, each vial must be reconstituted with its own kit. The total calculated dose can be rounded up or down to the nearest whole vial.

8.7.3 Description of Treatment

Subjects will be randomized to one of 2 PK-tailored prophylactic dose regimens (see Section 8.5) each of them targeting:

- FVIII trough levels of 1-3% with approximately twice weekly dosing, or
- FVIII trough levels of approximately 10% (8-12%) with dosing approximately every other day.

The individual subject's dose will be calculated by the sponsor and provided to the study site. Depending on subject's individual PK, different dosing intervals should be considered if single doses of >80 IU/kg are required or regular FVIII peak levels of 200% would be reached or exceeded.

8.7.4 BAX 855 Dosing for PK Assessment

Following a 72-96 h washout period, depending on the FVIII concentrate, subjects will undergo an initial PK assessment with BAX 855[vi]:

At Visit 9 months, i.e., after 9 months of prophylactic treatment with BAX 855, an optional repeat PK at steady state will be performed. No washout period will be required prior to the optional repeat PK determination; however, the PK infusion should preferably coincide with the prophylactic treatment schedule to ensure that the baseline FVIII trough level is reached.

The BAX 855 dose to be used for the PK assessment is 60 ±5 IU/kg. It must be administered in the hospital/clinic setting under medical supervision.

8.7.5 BAX 855 Prophylaxis Dosing

<u>FVIII trough level of 1-3%:</u>

BAX 855 will be administered twice weekly, with either:

- Infusion with alternating 3- and 4-day infusion intervals; the doses will be different if a 3- or a 4-day interval needs to be covered
- An infusion every 3.5 days
- Depending on subject's individual PK, different dosing intervals should be considered, in particular if single doses of 80 IU/kg are required or regular FVIII peak levels of 200% would be reached or exceeded

[vi] In case a subject underwent a PK determination in any of the BAX 855 studies, the PK assessment may have to be repeated based on the sponsor's evaluation.

FVIII trough level of approximately 10% (8%-12%):

- BAX 855 will be infused every other day.
- Depending on subject's individual PK, a different dosing interval may be considered to prevent regular high FVIII peak levels

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

The days of the week on which treatment is administered may be selected by the subject and/or his/her physician and should provide maximum coverage for vigorous activities. To provide some flexibility, the weekly schedule in terms of the days of the week may be changed during the course of the study to best accommodate potential changes in the subject's life style. However, the initially calculated and adjusted, if applicable, dose regimen should be maintained.

For each subject, the BAX 855 infusions to perform PK(s), IRs and the first individualized prophylaxis dose of BAX 855 at the Baseline visit, which includes an IR assessment, must be administered in the hospital/clinic setting under medical supervision. All other treatments may be self-administered, administered by a parent or caregiver, or administered in the clinic or hospital setting. Each subject's physician will determine the setting of treatment administration. If the subject will self-administer BAX 855, the investigator will ensure that the subject and/or his caregiver have been adequately trained.

The weight determined at baseline and subsequent study visits will be the basis for dose calculation of BAX 855 and recalculation, if applicable.

8.7.6 BAX 855 Dose and/or Frequency Adjustments

In the first 6-month treatment period the regimen may be adjusted based on the FVIII trough level determined at each study visit. FVIII trough levels should always be determined immediately before the planned next scheduled prophylactic infusion which may coincide with an infusion for determination of IR.

Before dose adjustment, if applicable, a confirmatory FVIII trough level determination at an additional study visit within 2 weeks after receipt of the FVIII activity results has to be

performed[vii]. This additional study visit should also occur after a washout period which is consistent with the infusion interval according to the treatment regimen provided to the subject and immediately before the next planned regular prophylactic infusion. After receipt of the repeat FVIII activity results, dose adjustments should be performed:

- If the lower FVIII trough activity level is <1% and <8% respectively;
- If the upper FVIII trough activity level exceeds 3% and 12% respectively. Given the assay variations, fluctuations of approximately 3% are possible.

Approximately 2 weeks after the dose adjustment, a repeat FVIII trough level determination at an additional study visit has to be performed, if it does not coincide with the next scheduled study visit. The blood draw for the FVIII trough level measurement should occur after a washout period consistent with the infusion interval according to the treatment regimen provided to the subject and immediately before the next planned regular prophylactic infusion.

Dose adjustments in the second 6-month period may only be performed if FVIII trough levels are considerably below the required FVIII trough levels of 1% and 8%. Should the upper limit considerably exceed 3% and 12% respectively, a dose adjustment may be performed. Dose adjustments should only be performed in case out-of-range FVIII trough value is confirmed with a repeat FVIII trough level measurement.

Guidance for dose adjustment:

- In case of FVIII levels <1% in the low dose arm, the dose should be increased by approximately 30%
- For FVIII levels >3% in the low dose arm, or FVIII levels >12% or <8% in the high dose arm, the adjusted dose for an infusion interval τ will be calculated as follows:

$$Dose_{adj,\tau} = \left(\frac{TL_{target}}{TL_{predicted,\tau}}\right) * Dose_{current,\tau}$$

where TL_{target} is the target trough level (1.7% or 10%) and $TL_{predicted,\tau}$ is the TL predicted for an infusion interval of τ under the current dose for this interval. The latter will be calculated as:

$$TL_{predicted,\tau} = 0.5 * \left(\frac{Dose_{current,\tau}}{Dose_1} * TL_{measured,t1} * 2^{\frac{t1-\tau}{HL}} + \frac{Dose_{current,\tau}}{Dose_2} * TL_{measured,t2} * 2^{\frac{t2-\tau}{HL}}\right)$$

[vii] This additional visit may coincide with regular scheduled study visit.

where $Dose_1$ and $Dose_2$ are the actual doses (in IU/kg) of the infusions after which the trough levels $TL_{measured,t1}$ and $TL_{measured,t2}$ were measured, t1 and t2 are the times in hours post start of infusion for each trough level collection, τ is the infusion intervals for which the prediction is being made, and HL is the terminal half-life of the initial PK assessment.

In case the FVIII levels are below the required lower limit, the BAX 855 dosage may be increased up to a maximum of 80 ±5 IU/kg and/or the dosing frequency may be increased. Doses as high as 80 IU/kg may be used, provided the FVIII peak level does not exceed 200%. Otherwise, the frequency of prophylactic infusions has to be increased.

In subjects with severe hemophilic arthropathy and/or target joints[viii] who continue to experience recurrent bleeding episodes, an imaging technology such as magnetic resonance imaging (MRI) or ultrasound of the affected joint(s) has to be applied to verify the presence of a bleed.

Also, if at any time during the course of the study, a subject starts to experience an unexpected high bleeding rate or experiences bleeding episodes that do not adequately respond to BAX 855 therapy, he/she will be evaluated for the presence of inhibitory and total binding antibodies to FVIII, BAX 855 and PEG, and clinically managed at the discretion of the investigator. It is also recommended to perform an IR determination.

8.7.7 Treatment of Bleeding Episodes

BAX 855 (10-60 ±5 IU/kg) will be used for treatment of bleeding episodes (i.e., breakthrough bleeding episodes during prophylaxis) according to the guidelines in Table 1. These guidelines may be adjusted by the investigator based upon his or her clinical judgment.

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

When bleeding is controlled, additional infusions of BAX 855 to maintain hemostasis are permitted, if required. Infusions given to maintain hemostasis should be documented in the eCRF.

For a detailed description of bleeding episodes into different sites see Section 23.

[viii] A target joint is defined as a single joint (ankles, knees, hips, or elbows) with ≥ 4 spontaneous bleeding episodes in any consecutive 6-month period.

Table 1
BAX 855 Treatment Guidelines for Bleeding Episodes

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

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

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

Whenever possible, the subject's most recent individual IR should be used. In its absence, an anticipated recovery of 2.0 (IU/dL)/(IU/kg) should be assumed and the required units calculated using the following formula:

body weight (kg) x desired FVIII rise (% or (IU/dL) x 0.5 dL/kg

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

In subjects with severe hemophilic arthropathy and/or target joints with recurrent bleeding requiring more than 2 infusions per bleed and/or where efficacy ratings are generally fair or none, an imaging technology such as MRI or an ultrasound of the affected joint(s) has to be applied to verify the presence of a bleed.

8.7.8 Treatment for Surgery or Dental Procedures

Subjects enrolled into this BAX 855 study (261303) and who require planned surgery or dental procedures will be treated according to the treatment recommendations including a FVIII substitution plan as described in Section 22. Subjects who undergo surgical procedures will only resume their PK tailored dosing regimen once rehabilitation requiring intensified treatment will be completed.

8.7.9 Investigational Product Accountability

The investigator will ensure that the IP (BAX 855) 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). 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.

8.8 Source Data

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

For additional information on study documentation and CRFs, see Section 18.2.
The use of subject diaries is described in Section 10.5.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

9.1.1 Subjects Transitioning from another BAX 855 Study

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

1. Subject has completed the end of study visit of a BAX 855 study or is transitioning from the ongoing Baxalta Continuation Study 261302
2. Subject is either receiving on-demand treatment or prophylactic treatment with BAX 855 and had an ABR of ≥2 documented and treated during the past 12 months
3. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥200 cells/mm^3, as confirmed by central laboratory
4. Subject is willing and able to comply with the requirements of the protocol

9.1.2 Inclusion Criteria for Newly Recruited Subjects

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

1. Subject is 12 to 65 years old at the time of screening
2. Subject has severe hemophilia A (FVIII clotting activity <1%) as confirmed by central laboratory OR by historically documented FVIII clotting activity performed by a certified clinical laboratory, optionally supported by a FVIII gene mutation consistent with severe hemophilia A
3. Subject has been previously treated with plasma-derived FVIII concentrates or recombinant FVIII for ≥150 documented EDs
4. Subject is either receiving on-demand treatment or prophylactic treatment and had an annual bleeding rate of ≥2 documented and treated during the past 12 months
5. Subject has a Karnofsky performance score of ≥60 at screening
6. Subject is HIV-; or HIV+ with stable disease and CD4+ count ≥200 cells/mm^3, as confirmed by central laboratory at screening
7. Subject is hepatitis C virus negative (HCV-) by antibody (if positive, additional PCR testing will be performed), as confirmed by central laboratory at screening; or HCV+ with chronic stable hepatitis
8. If female of childbearing potential, subject presents with a negative urine pregnancy test and agrees to employ adequate birth control measures for the duration of the study
9. Subject is willing and able to comply with the requirements of the protocol

9.2 Exclusion Criteria

9.2.1 Exclusion Criteria for Subjects Transitioning from Another BAX 855 Study

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

1. Subject has developed a confirmed inhibitory antibody to FVIII with a titer of ≥0.6 BU using the Nijmegen modification of the Bethesda assay as determined at the central laboratory during the course of the previous BAX 855 study
4. Subject has been diagnosed with an acquired hemostatic defect other than hemophilia A
5. The subject's weight is <35 kg or >100 kg
6. Subject's platelet count is <100,000/mL
7. Subject has an abnormal renal function (serum creatinine >1.5 times the upper limit of normal)
8. Subject has active hepatic disease with alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels ≥5 times the upper limit of normal
9. Subject is scheduled to receive a systemic immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day, or α-interferon) other than anti-retroviral chemotherapy during the study
10. Subject has a clinically significant medical, psychiatric, or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject's safety or compliance
11. Subject is planning to take part in any other clinical study during the course of the study
12. Subject is a member of the team conducting this study or is in a dependent relationship with one of the study team members. Dependent relationships include close relatives (i.e., children, partner/spouse, siblings, parents) as well as employees of the investigator or site personnel conducting the study.

9.2.2 Exclusion Criteria for Newly Recruited Subjects

Newly recruited subjects who meet **ANY** of the following criteria are not eligible for this study:

1. Subject has detectable FVIII inhibitory antibodies (≥0.6 BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening
2. Subject has a history of confirmed FVIII inhibitors with a titer ≥0.6 BU (as determined by the Nijmegen modification of the Bethesda assay or the assay employed with the respective cut-off in the local laboratory) at any time prior to screening

3. Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (e.g., qualitative platelet defect or von Willebrand's disease)
4. The subject's weight is <35 kg or >100 kg
5. Subject's platelet count is <100,000/mL
6. Subject has known hypersensitivity towards mouse or hamster proteins, PEG or Tween 80
7. Subject has severe chronic hepatic dysfunction [e.g., ≥5 times upper limit of normal ALT and/or AST, as confirmed by central laboratory at screening, or a documented INR >1.5]
8. Subject has severe renal impairment (serum creatinine >1.5 times the upper limit of normal)
9. Subject has current or recent (<30 days) use of other pegylated drugs prior to study participation or is scheduled to use such drugs during study participation
10. Subject is scheduled to receive during the course of the study, a systemic immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day, or α-interferon) other than anti-retroviral chemotherapy
11. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
12. Subject has a medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance
13. Subject is a member of the team conducting this study or is in a dependent relationship with one of the study team members. Dependent relationships include close relatives (i.e., children, partner/spouse, siblings, parents) as well as employees of the investigator or site personnel conducting the study.

9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., 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 termination visit (including in cases of withdrawal or discontinuation) are described in Section 10.6 and Section 21.3.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., 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 will be withdrawn from treatment or discontinued from further study participation for the following reasons:

- The subject develops a confirmed high responder inhibitory antibody to FVIII (>5 BU by Nijmegen modification of the Bethesda assay) or a low responder inhibitory antibody (≤5 BU but ≥0.6 BU) that cannot be managed by the protocol-required prophylactic dosing.
- The subject experiences a severe anaphylactic reaction to BAX 855
- The subject requires therapy with another pegylated product (e.g., PEG-Interferon)
- The subject frequently misses administration of IP (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 and/or sponsor
- The subject uses his/her usual FVIII therapy following the baseline infusion
- The subject requires major emergency surgery during this study
- The subject experiences a life-threatening bleeding episode (e.g., any gastrointestinal hemorrhage or intracranial hemorrhage) requiring the use of a FVIII concentrate other than BAX 855
- The subject experiences severe trauma requiring extensive FVIII replacement therapy other than BAX 855

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any subject, or their legal representatives, as required, who provides informed consent (i.e., signs and dates the informed consent form and assent form, if applicable) is considered enrolled in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (i.e., 261303) to be provided by the sponsor, 3-digit number study site number (e.g., 002) to be provided by the sponsor, and 3-digit subject number (e.g., 003) reflecting the order of enrollment (i.e., signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 261303-002003. All study documents (e.g., 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 (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. If a subject does not satisfy all screening criteria, the same subject may be re-screened at a later date. A complete or partial re-screen may also become necessary at the discretion of the investigator or sponsor. All screening data will be collected and reported in eCRFs, regardless of screening outcome. For the purpose of analysis, only the data from the most recent screening visit will be used. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The screening procedures including laboratory evaluations must be completed within 56 days or repeated if more than 56 days have elapsed. Exemptions may be granted for administrative reasons, e.g., delay in timely availability of laboratory results.

The overall study design is illustrated in the Figure 1. Details on the procedures to be performed at each study visit, including screening, can be found in Section 21.2 Detailed Flow Diagram of Study Procedures, Section 21.3 Schedule of Study Procedures and Assessments, and Section 21.4 Clinical Laboratory Assessments. Only explanatory details are provided in the following section.

10.3.1 Subjects Transitioning from Other BAX 855 Studies

Subjects transitioning from other BAX 855 studies[ix] can use the end of study assessments in their previous BAX 855 study for screening visit assessments in this PK-guided study. Any additionally required screening assessments will be performed the same day. Subjects will return to the study site no later than 56 days for the conductance of the PK assessment, if applicable, provided eligibility has been confirmed. At the screening visit the subject will be supplied with study IP of study 261303. Until the baseline visit subjects will be treated according to their previous BAX 855 treatment regimen.

10.3.2 Newly Recruited Subjects

Newly recruited subjects will continue using their FVIII treatment regimen until baseline/start of PK-guided prophylaxis, except for one infusion with BAX 855 for PK determination.

10.4 Medications and Non-Drug Therapies

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

- Medications:
  - Any pegylated medication (e.g., PEG-interferon) except BAX 855 for transitioning subjects
  - Any investigational drug, biologic, or device except BAX 855 for transitioning subjects

A subject who has taken any of these medications or received any of these non-drug therapies will be considered a protocol deviation.

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

[ix] For subjects in the continuation study, data from a regular scheduled study visit can be used as long they are not older than 4 weeks prior to screening.

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

- Medications:
  - Hemostatic agents, such as tranexamic acid, are permitted, as indicated by the subject's treating physician, to treat mucosal bleeding or during perioperative management 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 (e.g., physiotherapy) deemed necessary by the subject's physician to treat or prevent any medical condition

10.5 Subject Diary and Patient Reported Outcomes

A subject diary will be provided to each subject at the Screening Visit to record the following information:

1. Infusion record for BAX 855
2. Details of bleeding episodes and response to treatment. For a detailed description of bleeding episodes into different sites see Section 23.
3. Physical activity within 8 h prior to the occurrence of a bleeding episode
4. Type and duration of physical activity with a risk category of 2.5 or higher [29] or contact sport with a duration of ≥15 minutes
5. Untoward events
6. PROs (see Section 10.5.1)

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

- Location of bleed, e.g., joint, soft tissue, muscle, body cavity, intracranial, other
- Type of bleed, i.e., spontaneous (i.e., not related to injury/trauma), injury (definitely due to injury/trauma)
- Severity of bleed, e.g., minor, moderate, major (see Table 1)
- Date and time of onset of bleed

- Date and time of each infusion of BAX 855 required to achieve adequate hemostasis
- Date and time of resolution of bleeding episode
- Overall clinical efficacy rating according to the rating scale as described in Table 2 at 8 (±1) hours after initiation of treatment and at resolution of bleed
- Physical activity within 8 h prior to the occurrence of the bleeding episodes

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic or paper format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner. Untoward events recorded in the diary will be reported as AEs according to the investigator's discretion and clinical judgment. Subject entries in the diary will serve as source records. If e-diaries are used, during study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the CRF by a validated transfer.

10.5.1 Patient Reported Outcomes

The PRO instruments to be measured in this study are described below. These measures will be administered in this study at 3 timepoints: Screening or Baseline Visit, 6-month visit, and Completion/Termination Visit, whereas the EQ-5D, Patient Activity Level, and Health Resource Use will be measured at each study visit before study specific procedures are started. Note that due to the unavailability of linguistically validated translations of certain PRO measures in certain countries, some of these questionnaires may not be administered in all countries participating in this study. In addition, subjects who are younger than the minimal age limit required for these assessments will not be required to complete the assessment.

1. **Haemo-SYM Questionnaire** – This is a self-administered, validated questionnaire designed to assess symptom severity in subjects 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.
2. **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.

3. **EQ-5D Questionnaire** – The EQ-5D is a self-administered, standardized measure of health status that provides a generic measure of health for clinical and economic appraisal consisting of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression each with 3 levels. There is an additional EQ visual analog scale to record how good or bad their health state is.
4. **Patient Activity Level**
   Subjects will also be asked to estimate their activity levels. This will consist of a few questions asking subjects to rate their current level of activity. These data will be collected for all age groups.
5. **Health Resource Use** – For each occurrence (throughout the study), the subject 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), and hospitalizations (reason, dates of hospitalization and associated length of stay).

10.6 Subject Completion/Discontinuation

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

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on 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 Section 21.2 Detailed Flow Diagram of Study Procedures, Section 21.3 Schedule of Study Procedures and Assessments, and Section 21.4 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.7 Procedures for Monitoring Subject Compliance

Subject compliance with the BAX 855 individualized treatment regimens will be monitored by review of subject diaries and by IP accountability.

11. ASSESSMENT OF EFFICACY

11.1 Bleeding Assessment

Each individual bleed, spontaneous or traumatic, will be recorded in the subject's diary, and/or recorded in physician/nurse/clinic notes. A bleed is defined as subjective (e.g., pain consistent with a joint bleed) or objective evidence of bleeding which may or may not require treatment with FVIII. For further definitions of bleeds see Section 23. Bleeds occurring at the same anatomical location (e.g., right knee) with the same etiology (i.e., spontaneous vs. injury) within 72 h of onset of the first bleed will be considered a single bleed.[30] A new bleed is defined as a bleed occurring >72 hours after stopping treatment for the original bleed for which treatment was initiated and had an initial moderate to excellent response to treatment.[30] Bleeding occurring at multiple locations related to the same injury (e.g., knee and ankle bleeds following a fall) will be counted as a single bleeding episode.

The subject will also indicate in the diary on a preselected scale the type of activity within 8 hours prior to the bleeding episode.

For the primary assessment, the total bleed rate in the second 6-month study period will be calculated (i.e., after the 6-month visit to the Completion/Termination Visit). The secondary outcome measures, spontaneous and traumatic ABR, and spontaneous AJBR will also be calculated from the recorded bleeds.

11.1.1 Hemostatic Efficacy Rating for Treatment of Bleeding Episodes

The subject or their caregiver will rate the severity (minor, moderate, or major) of the bleeding episode and will rate the overall treatment response at 8 (±1) hours after the initiation of treatment and at the resolution of bleed using a 4-point efficacy rating scale (Table 2). Since the efficacy rating is based to a large degree on cessation of pain, the investigator/subject shall, in particular in case of injury-related bleeding into one or more than one location, consider the injury-related symptoms when performing the efficacy rating 8 (±1) hours after initiating treatment and at resolution of bleed.

As per Table 2, multiple infusions of BAX 855 may be administered for the treatment of a bleeding episode. The overall response to all infusions combined is the rating that will be recorded at resolution of bleed.

Table 2 Efficacy Rating Scale for Treatment of Bleeding Episodes	
Excellent	Full relief of pain and/or cessation of objective signs of bleeding (e.g., 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	Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution.
None	No improvement or condition worsens.

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

- Any inconsistency between the efficacy rating and the number of infusions used to treat a bleeding episode, or a response to treatment rated as "none" must be immediately clarified.
- If 2 or more responses to treatment of unique bleeding episodes are rated "fair", the investigator may re-evaluate the dosing regimen and the time from bleeding onset to the start of treatment. If a bleeding episode requires only one infusion but response to treatment is rated "fair", the rating should be evaluated and the Rating Scale should be reviewed with the subject/subject's caregiver.

If more than one infusion was given to treat a bleeding episode, and the treatment was rated "excellent", additional information should be provided about the severity of the bleeding episode (see Table 1) and/or whether additional infusions were given to maintain hemostasis. If infusions were given to maintain hemostasis after resolution of bleed, this should be recorded accordingly in the eCRF.

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

The number of BAX 855 infusions needed for each bleeding episode depends on the severity and location of the bleed and is determined by the subject, his/her caregiver, and/or clinician treating the subject, and is based upon the subject's response to treatment, using the Efficacy Rating Scale for Treatment of Bleeding Episodes in Table 2. An infusion is defined as completion of administration of the calculated dose of BAX 855. If an infusion is interrupted, e.g., 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 not completing the infusion will be recorded.

11.1.3 Hemophilia Joint Health Score (HJHS)

The HJHS will be assessed at Baseline, i.e., the first PK-guided prophylactic infusion with BAX 855, and the completion/termination visit. The PI or a qualified staff member (e.g., physiotherapist) will assess the following components of the elbow, knee, and ankle joints: swelling, duration of swelling, muscle atrophy, crepitus on motion, flexion loss, extension loss, joint pain, and strength, together with an assessment of the global gait.

11.1.4 X-ray of Impaired Joints

At Baseline, or at Week 4 ±5 days at the latest, an X-ray of an impaired joint evaluated as part of the HJHS will be taken if 1 or more items of the HJHS has a scoring of 1 or more. If an X-ray of the impaired joint is already available and not older than 12 months, it does not have to be repeated. The description of the radiological findings of the impaired joint should be according to the "Radiologic Classification of Changes"[31] (see Section 23.3) and the respective joint score indicated.

11.1.5 Weight-Adjusted Consumption of BAX 855

Weight-adjusted consumption of BAX 855 will be determined based upon the record in subjects' diaries of the amount of BAX 855 infused and the subject's weight, as measured in the clinic.

11.1.6 Peri-operative efficacy assessments

For the detailed description of intra-, post- and perioperative efficacy see Section 22.

12. DETERMINATION OF FVIII AND VWF ANTIGEN, FVIII ACTIVITY AND TGA

12.1 PHARMACOKINETICS

An initial evaluation of PK parameters based on FVIII activity will be performed in all subjects prior to randomization[x]. This PK will be performed following a washout period of at least 72-96 hours, depending on the type of FVIII concentrate used.

In all subjects, an optional repeat PK evaluation will be performed at the 9 month ±2 weeks visit to assess PK at steady state. For the repeat PK, no washout period will be required and the PK infusion should coincide with the timepoint of a scheduled prophylactic infusion to ensure that the trough FVIII activity level has been obtained.

Samples will be taken to assess FVIII activity, FVIII antigen and TGA parameters pre-infusion and at several timepoints post-infusion over a 4-day period following a single dose of 60 ±5 IU/kg of BAX 855. VWF antigen will be also determined from the pre-infusion blood sample.

Blood samples are collected at the following timepoints:

Table 3
PK Timepoints

		FVIII (Activity and Antigen)	VWF Antigen	TGA
Pre-infusion	Within 30 minutes prior to infusic	+	+	+
Infusion	60 ±5 IU/kg of BAX 855			
Post-infusion	15–30 minutes	+		+
	3 hours ±30 minutes	+		+
	8 hours ±30 minutes	+		+
	24 hours ±2 hour	+		+
	48 hours ±4 hour	+		+
	72 hours ±4 hour	+		+
	96 hours ±4 hour	+		+

[x] In case a subject underwent a PK determination in BAX 855 surgery or continuation study, the PK assessment may have to be repeated based on the sponsor's evaluation.

The PK infusion may be administered via a central line or a peripheral vein. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution. All PK samples will be collected through a peripheral vein. Blood samples drawn during the first 3 hours after BAX 855 administration will be drawn from a peripheral vein in an extremity distinct from the one that was used for product infusion. After that time, a vein in any appropriate extremity may be used. In the event that a blood sample must be drawn through the central or peripheral line used for administration of IP, the line must first be flushed with 5 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the blood sample.

For further details regarding analysis of FVIII activity see Section 13.8.3.

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

12.2 Incremental Recovery (IR)

IR will be determined at each study visit except study visit Week 4 ±5 days, Week 8 ±1 week, and Month 4.5 ±2 weeks when only trough levels will be measured. Following a washout period required for the respective treatment group, blood samples for the determination of IR will be taken at the following timepoints:

Table 4
IR Time Points

		FVIII (Activity and Antigen)	VWF Antigen	TGA
Pre-infusion	Within 30 minutes prior to infusion	+	+	+
Infusion	PK-guided prophylactic dose of BAX 855			
Post-infusion	15 -30 minutes	+		+

12.3 Trough Levels

At study visit Week 4 ±5 days, Week 8 ±1 week, and Month 4.5 ±2 weeks, FVIII activity trough levels will be measured to ensure that FVIII trough levels are within their targeted range. The blood sampling for FVIII activity, TGA parameters and VWF antigen should be performed immediately prior to the next regular prophylactic infusion, thus maintaining the treatment regimen-specific interval defined for each subject. Following dose adjustments, a FVIII trough level has to be determined approximately 2 weeks following the dose adjustment.

Details on the sampling of blood for determination of FVIII trough levels are presented in Section 21.3 and Section 21.4.

13. ASSESSMENT OF SAFETY INCLUDING IMMUNOGENICITY

13.1 Immunogenicity

Immunogenicity of BAX 855 will be assessed prior to the infusion of BAX 855 following a washout period[xi] by measurement of the following antibodies (see also Section 21.4 for the timepoints):

- Inhibitory antibodies to FVIII, using 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 enzyme-linked immunoabsorbent assay (ELISA) assay
- Anti-CHO antibodies measured by an ELISA assay

In addition to the timepoints as described in Section 21.4, the subject should be evaluated for inhibitory and binding antibodies to FVIII, BAX 855, and PEG if clinically indicated, e.g., lack of response to treatment.

A low titer (responder) inhibitor is defined as ≥0.6 BU but ≤5 BU. A high titer (responder) inhibitor is defined as >5 BU by Nijmegen modification of the Bethesda assay. Inhibitors must be documented at 2 separate timepoints within a 2- to 4-week period at a central laboratory. Every confirmed FVIII inhibitor ≥0.6 BU at the central laboratory must be reported as an SAE.

Based on the variability of the binding antibody tests, only samples with titers ≥1:80 can be confirmed and will be evaluated as positive.

FVIII IgG subclass 1-4 and IgA (using ELISA) may be assessed only if clinically indicated, e.g., in case of lack of response to treatment. IgE antibodies to FVIII and PEG-FVIII (using ImmunoCaps, Thermo Fisher) may be assayed as clinically indicated, e.g., in case of hypersensitivity reactions.

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.

All assays will be performed in a central laboratory.

[xi] The washout period will be consistent with the infusion interval according to the treatment regimen provided to the subject.

13.2 Adverse Events

13.2.1 Definitions

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

13.2.1.1 Serious Adverse Event

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

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
    - Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)
    - Development of a confirmed inhibitor to FVIII with an inhibitor level ≥0.6 BU, as measured by the Nijmegen modification of the Bethesda assay at the central laboratory
    - Severe hypersensitivity/allergic reactions to BAX 855

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

13.2.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment (i.e., including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Once determined to meet the criteria for a SUSAR, the sponsor will ensure expedited SUSAR reporting in line with the regulatory requirements in participating countries.

13.2.1.3 Non-Serious Adverse Event

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

13.2.2 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 (e.g., 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, all AEs including unexpected AEs experienced by a subject undergoing study treatment will be recorded on the AE CRF.

13.2.3 Preexisting Diseases

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

13.2.4 Assessment of Adverse Events

For the purposes of this study, the following non-serious events experienced after the first IP exposure will not be considered AEs, 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 but for which the subject was hospitalized
- Hospitalizations for planned medical or surgical procedures, e.g., placement of a central venous line (however, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF)
- Hospitalization or prolongation of hospitalization intended only for social reasons.
- Seroconversion after documented HAV/HBV vaccination prior to or during the study period
- Bleeding episodes/hemophilia-related events: Bleeding episodes are part of the underlying disease and therefore are not AEs. If a bleeding episode was caused by an injury (e.g., a fall), the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (e.g., abrasion of skin; fractured tibia). Therefore, any hemophilia-related event (e.g., hemarthrosis, bruising, hemorrhage) will not be reported as an AE, but these events will be recorded on the bleeding event CRF. However, hemophilia-related events meeting the criteria for seriousness (e.g., a gastrointestinal hemorrhage requiring hospitalization) will be reported as SAEs and described on the SAE report

All other AEs from the first IP exposure until study completion/discontinuation will be described 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 13.2). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 13.2.1.1
- Severity as defined in Section 13.2.5
- Causal relationship to IP exposure or study procedure as defined in Section 13.2.6

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (i.e., 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. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

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

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

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

13.2.5 Severity

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.

13.2.6 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, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not associated with the IP (i.e., 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 re-challenge)
    - 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, and occurring within 24 hours of IP administration, 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.

13.2.7 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Section 21.3).

Adverse events/SAEs are to be recorded on the AE page of the eCRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the investigational product, must be reported immediately (within 24 hours of the study site's first knowledge of the event). All SAEs must be reported via the Electronic Data Capture (EDC) system by completing the relevant electronic Case Report Form (eCRF) page(s) in English. For instances in which the EDC may become unavailable, SAEs must be reported using the back-up paper SAE Report Form to meet the 24-hour timeline requirement (for contacts and instructions refer to the SAE Report Form). Once the EDC becomes available, the site must enter all SAE data as reported on the back-up paper SAE Report Form on the applicable eCRF pages.

The initial SAE information reported on the applicable eCRF pages (or back-up SAE Report Form, if applicable) must at least include the following:

1. Protocol Number
2. Subject identification number and demographics (gender, age at onset of event, and/or date of birth)
3. Investigational product exposure
4. Medical Term for Event (Diagnosis preferably)
5. Description of the (S)AE, including:
   - Date of onset
   - (S)AE treatment (drug, dose, route of administration)
   - Causal relationship by the Investigator
   - Measures taken (i.e., action taken regarding investigational product in direct relationship to the AE)
6. Seriousness criteria (i.e., death, life-threatening, or other criterion)

7. Cause of death
8. Autopsy findings (if available)
9. Name, address, fax number, email, and telephone number of the reporting Investigator (for paper SAE Report Forms)

13.2.8 Medical Device Safety Reporting

The IP kit contains the BAXJECT device. All Serious Injuries and Unexpected Adverse Device Events must be reported to the sponsor as an SAE in the same process as described above.

Serious injury is defined as:

1. Life-threatening injury or illness results in permanent impairment/ damage to body function/ structure
2. Requires medical or surgical intervention to preclude permanent impairment/ damage to body function/ structure

13.3 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.

13.4 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 13.2). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the AE CRF (and SAE Report Form if eCRF is not available). 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 procedures (e.g., during blood sampling) 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.

13.5 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:

1. A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g., reconstitution difficulty
2. Missing components
3. Damage to the product or unit carton
4. A mislabeled product (e.g., potential counterfeiting/tampering)
5. A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

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

13.6 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 13.2.5) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

The historical ABR including treated and untreated bleeding episodes in the 12 months prior to study enrollment based on medical records should also be recorded in the eCRF. Only the treated bleeds will be the basis for inclusion in the study.

All medications taken and non-drug therapies received from 4 weeks 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 eCRF.

13.7 Physical Examinations

At screening and subsequent study visits (as described in the schedule in Section 21.2), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At screening, the Karnofsky performance score will be assessed.

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 13.2.3), 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.

13.8 Clinical Laboratory Parameters

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

At all laboratory assessments subjects must not be actively bleeding. In addition to the laboratory assessments planned in the protocol, appropriate clinical laboratory testing should be performed whenever clinically indicated.

Details on the visits and timing of blood sampling for the laboratory parameters are provided in Section 21.2 and Section 21.3.

13.8.1 Screening Laboratory Parameters

13.8.1.1 Blood Type

For subjects who do not have documentation of their blood type in their medical record, blood ABO blood type will be measured locally at screening.

13.8.1.2 Genetics and HLA-Genotype

FVIII gene mutation analysis and HLA genotype will be analyzed at screening. If results of FVIII gene mutation analysis and HLA genotype are already available at the study site, they will be provided to the sponsor and a reanalysis will not be required in those subjects.

13.8.1.3 Pregnancy Test

A pregnancy test should be performed as appropriate (serum pregnancy test in females of child-bearing potential if no urine sample is available). The pregnancy test might be repeated during the study in countries where mandated by national law.

13.8.1.4 CD4 Count

At screening only, CD4 levels will be determined in all HIV+ subjects using flow cytometry.

13.8.1.5 Viral Serology

Viral serology testing will include HIV-1 and HIV-2 antibody, HBsAb, HBsAg, HBcAb, and HCV Ab. HCV titer will be confirmed by PCR for all subjects reported as HCV positive. All assessments will be performed at screening only, or if clinically indicated. A positive test for HBsAg will be repeated using a new blood sample.

13.8.2 Hematology, Clinical Chemistry and Lipid Panel

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

The hematology panel consists of complete blood count [hemoglobin, hematocrit, erythrocytes (i.e., red blood cell count), and leukocytes (i.e., white blood cell count)] with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and platelet count.

The clinical chemistry panel consists of sodium, potassium, chloride, bicarbonate, total protein, albumin, ALT, AST, total bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, and glucose.

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

13.8.3 FVIII Activity, FVIII Antigen, VWF Antigen

Blood samples will be analyzed for FVIII activity (1-stage clotting assay and the chromogenic assay) at a central laboratory. The 1-stage clotting assay will serve as the primary assay; the chromogenic assay will be used to provide supportive data. In addition FVIII antigen will be measured by ELISA. VWF antigen will be determined using ELISA from pre-infusion samples. The detailed timepoints of FVIII activity, FVIII antigen and VWF antigen assessment are provided in Section 12.1, Section 12.2, and Section 21.4.

13.8.4 Thrombin Generation Assay

For TGA parameters (lag time, time to peak thrombin generation, peak thrombin generation, and endogenous thrombin potential [ETP]), plasma samples will be tested using the calibrated, automated thrombin generation method (CAT). For details on the individual timepoints for TGA assessment please see Section 12.1, Section 21.2, and Section 21.4.

13.8.5 Assessment of Laboratory Values

13.8.5.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each laboratory value (i.e., hematology, clinical chemistry, and lipids) will 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 13.2, 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 13.2.3), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e., because it is due to a preexisting disease, due to a lab error, or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

13.8.6 Biobanking

Subjects will consent for taking an extra blood sample at each study visit for additional analysis, if necessary. Backup samples that remain after study testing is done may be stored and used for additional testing (e.g., further evaluation of an abnormal test or an AE).

Also, an additional blood draw for further exploratory testing, i.e., biomarkers for hemophilia, will be drawn pre-infusion and early in the morning , if feasible, otherwise at the same timepoint at the Baseline, Month 3, Month 6, Month 9, and Completion/Termination study visit (see Clinical Laboratory Assessment Schedule in Section 21.4).

Samples will be stored in a coded form for no more than 2 years after the final study report has been completed and then the samples will subsequently be destroyed.

13.9 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 (in or cm) and weight (lb or kg) will also be collected at screening; weight will also be recorded before any IP infusions are administered at the study site, but at least at each study visit. Blood pressure will be measured when subjects are in the supine position.

Vital signs will be assessed within 15 minutes prior to start of infusion and 30 ±5 minutes following infusion at baseline and at each study visit. Vital signs should always be assessed before any blood sampling is done at a particular timepoint.

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 13.2 and record the medical diagnosis (preferably), symptom, or sign on the AE CRF). Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

14. STATISTICS

14.1 Sample Size and Power Calculations

14.1.1 Sample Size Calculation

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

Under these assumptions 48 subjects per study arm are needed to reject the null hypothesis of no difference between the study arms against a 2-sided alternative at the 5% level of statistical significance with 80% power. Assuming a drop-out rate of close to 10%, and 10-15% of subjects being non-compliant, approximately 116 subjects are planned to be randomized between the 2 BAX 855 regimens with an allocation ratio of 1:1.

14.2 Datasets and Analysis Cohorts

14.2.1 Full Analysis Set

The Full Analysis Set will comprise all subjects who were randomized and who were treated with BAX 855 prophylactically for any period of time.

14.2.2 Per Protocol Analysis Set

The Per Protocol Analysis Set will comprise all subjects who were randomized and completed the second 6 months of prophylactic treatment.

14.2.3 Safety Analysis Set

The Safety Analysis Set (SAS) will comprise all subjects treated with at least 1 BAX 855 dose. All safety analyses for BAX 855 will be performed on the SAS.

14.3 Handling of Missing, Unused, and Spurious Data

Missing data will not be imputed in general, with the exceptions as detailed below.

14.3.1 Handling of incomplete observation periods for ABR

The primary endpoint requires complete data for the second 6 months of prophylaxis (Day 183 to Day 364). The multiple imputations technique will be used for the analysis of the primary endpoint and estimation of ABRs. As this is a statistical analysis technique, it will be described in the statistical analysis section.

14.3.2 Handling of other variables

If body weight is missing for a subject then the last value of available body weight measurement will be carried forward in order to compute weight-adjusted BAX 855 consumption. If the date of onset for an AE is missing completely then it will be imputed with the date of the first study drug application.

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

Regarding missing data in AE records:

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

14.4 Methods of Analysis

14.4.1 Primary Outcome Measure

The proportion of subjects with ABR = 0 in the 2 prophylaxis treatment regimens in the second 6 months period will be compared using a chi-square test with continuity correction at a 2-sided 5% level of significance.

The null hypotheses of no difference between the prophylactic regimens will be tested against a 2-sided alternative.

The observation period for the primary endpoint will be the second 6 months of prophylaxis (Day 183 to Day 364). If the subject undergoes a surgical procedure the observation period is interrupted starting from the presurgical loading dose until the subject resumes his previous prophylactic treatment regimen, or until rehabilitation or any other surgery specific postoperative measures have been completed, whichever occurs last.

Data analyses will follow the intent-to-treat principle, i.e., bleedings observed in the observation period will be used in the analyses irrespective of compliance with the treatment regimen of the protocol. Only if a subject refuses to provide any bleeding data, the multiple imputations (MI) technique will be used to handle observation periods shorter than 6 months, i.e., 182 days, as follows.

For subjects who terminated before Day 364 and refuse to provide data on bleeds, bleeds will be imputed for the unobserved period from a Poisson random variate. The subject specific Poisson parameter will be determined from estimating a negative binomial model for the bleed rate in the unobserved period with stratum, age, race as well as the number of bleeds from Day 92 to the end of the observed period of the subject as covariates in all subjects of the same Study Arm. For subjects with more than 21 weeks in the observation period, the number of bleeds occurring at a later time in other subjects might be very low or even zero. To avoid estimating from an unstable model, the negative binomial model will be for the number of bleed up to Day 329 with covariates of stratum, age, race and number of bleeds observed from Day 92 to Day 329. At least 1000 imputation datasets will be generated. The chi-squared test statistics with continuity correction and its standard error will be used to compare the 2 study arms in each imputation dataset and the multiple imputations techniques will be used to derive an overall estimate with 2-sided 95% CIs.

The dataset to be analyzed is all subjects. For subjects who developed an inhibitor, missing observation periods will be imputed at twice the rate before the study.

The use of age and race in the imputation model will allow for subgroup analyses of the primary endpoint and ABRs.

Sensitivity analyses

Sensitivity analyses will be performed similar to the primary analysis except that the negative binomial distributions used for imputations will have an artificially increased Poisson parameter by 10%, 20%, 40% and 80%. In addition, a worst-case sensitivity analysis will be performed which imputes worst-case outcomes in all subjects with missing ABR data in the observation period.

14.4.2 Secondary Outcome Measures

- Total, spontaneous, and traumatic ABR, and spontaneous AJBR

For total ABR, spontaneous ABR, traumatic ABR and spontaneous JABR, separate negative binomial models will be used for the second 6 months treatment period (Days 183 to 364) as well as for the complete 12-month treatment period (Days 1 to 364).

The negative binomial model for the bleed rate will include covariates for study arm, stratum, age, and race. The multiple imputations technique will be used for incomplete observation periods as described for the primary endpoints analysis. Subgroups for age and race will be analyzed as well.

For all other outcome measures, descriptive statistics will be presented for the 2 dosing regimens. Point estimates (means and medians) and their 95% CIs will be computed to include:

- Total weight-adjusted consumption of BAX 855 for each prophylactic regimen
- Overall hemostatic efficacy rating at 8 ±1 h after initiation of treatment and at resolution of bleed
- Number of BAX 855 infusions needed for the treatment of bleeding episodes
- HJHS
- Physical domain and component scores of the SF-36
- Physical Activity Levels

In case of surgeries, descriptive statistics will be performed for the following secondary outcome measures:

- Intra-, post- and perioperative hemostatic efficacy in case of surgery (see Section 22.5.1 for details)
- Intra- and postoperative blood loss in case of surgery (see Section 22.5.2 for details)

PK parameters before randomization will be summarized descriptively over all subjects to include:

- $AUC_{0-\infty}$, IR at 15-30 minutes post-infusion, $T_{1/2}$, MRT, CL, Cmax, Tmax, and V_{ss}

PK parameters after 9 months will be summarized descriptively by prophylactic treatment regimen:

- $AUC_{0-\infty}$, IR at 15-30 minutes post-infusion, $T_{1/2}$, CL, Cmax, and Tmax
- IR over time will be displayed as boxplots for the 2 prophylactic regimens

Correlation of VWF:Ag and PK parameters will be assessed by boxplots and Spearman rank correlation coefficient.

Descriptive statistics will be used for the secondary safety outcome measures (see Section 8.4.2.2):

- Occurrence of AEs and SAEs

- Changes in vital signs and clinical laboratory parameters (hematology, clinical chemistry, and lipids)
- Inhibitory antibodies to FVIII, and binding antibodies to FVIII, BAX 855, PEG, and CHO protein

The methods of analysis for the secondary PROs measures (see Section 8.4.2.3) are described for the following PROs:

- Physical domain and component scores of the SF-36
- Physical activity levels

Change scores from baseline to completion/follow-up will be assessed for each treatment arm and tested using the minimally important difference threshold and the Wilcoxon sign rank test. Differences in the change scores between treatment groups will be tested using the minimally importance difference threshold and the Mann-Whitney U Test.

14.4.3 Exploratory Outcome Measures

Boxplots and Spearman rank correlation coefficient will be used to assess the correlation between the average of various coagulation parameters (TGA parameters: lag time, time to peak thrombin generation, peak thrombin generation, and endogenous thrombin potential [ETP] and FVIII trough levels) and ABR in the same time periods (first 6 months, second 6 months, overall).

Changes from baseline to completion/follow-up for subjects for the 2 dosing arms will be tested using the minimally importance difference threshold and the Wilcoxon sign rank test for the following PROs:

- Bleed and pain severity as measured by the Haemo-SYM questionnaire
- HRQoL as assessed using the EQ-5D and mental domain and component scores of the SF-36 questionnaire
- Health Resource Utilization

Differences in the change scores between treatment groups will be tested using the minimally importance difference threshold and the Mann-Whitney U Test for the following PROs:

- Bleed and pain severity as measured by the Haemo-SYM questionnaire
- HRQoL as assessed using the EQ-5D and mental domain and components scores of the SF-36 questionnaire
- Health Resource Utilization

15. 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 Trial Agreement (CTA). 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 CTA.

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable national and local regulatory requirements as described in the CTA. The trial will also be conducted in accordance with the Helsinki declaration. 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.

16.1.1 Final Clinical Study Report

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

16.2 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.

16.3 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 national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

16.4 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 national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the CTA. Auditing processes specific to the study will be described in the auditing plan.

16.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible EC and relevant competent authority 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.

16.6 Laboratory and Reader Standardization

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

17. ETHICS

17.1 Subject Privacy

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

17.2 Ethics Committee and Regulatory Authorities

Before enrollment of subjects 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 CTA.

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.

17.3 Informed Consent

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

All subjects and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable national and local regulatory requirements and ICH GCP. An assent form may be provided and should be signed by subjects less than 18 years of age. Before use, the informed consent/assent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 17.2). The informed consent/assent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Subjects and/or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent/assent form, subjects and/or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent/assent will be updated, if necessary. This new information and/or revised informed consent/assent form that have been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects and/or the subjects' legally authorized representative who consented to participate in the study (see Section 17.3).

17.4 Data Monitoring Committee

A Data Monitoring Committee (DMC) will not be used for this study as the expected related AEs in this study are anticipated to be similar to that of the licensed product ADVATE (of which the core protein is identical to that of BAX 855; see Section 6.5 for more details on anticipated risks and benefits of BAX 855). Additionally, the safety is not expected to differ from the safety observed in the BAX 855 pivotal and the ongoing BAX 855 continuation study (Studies 261201 and 261302, respectively).

18. DATA HANDLING AND RECORD KEEPING

18.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the CTA.

18.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.8), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, 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 18.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., 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.

18.3 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 CTA.

19. FINANCING AND INSURANCE

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

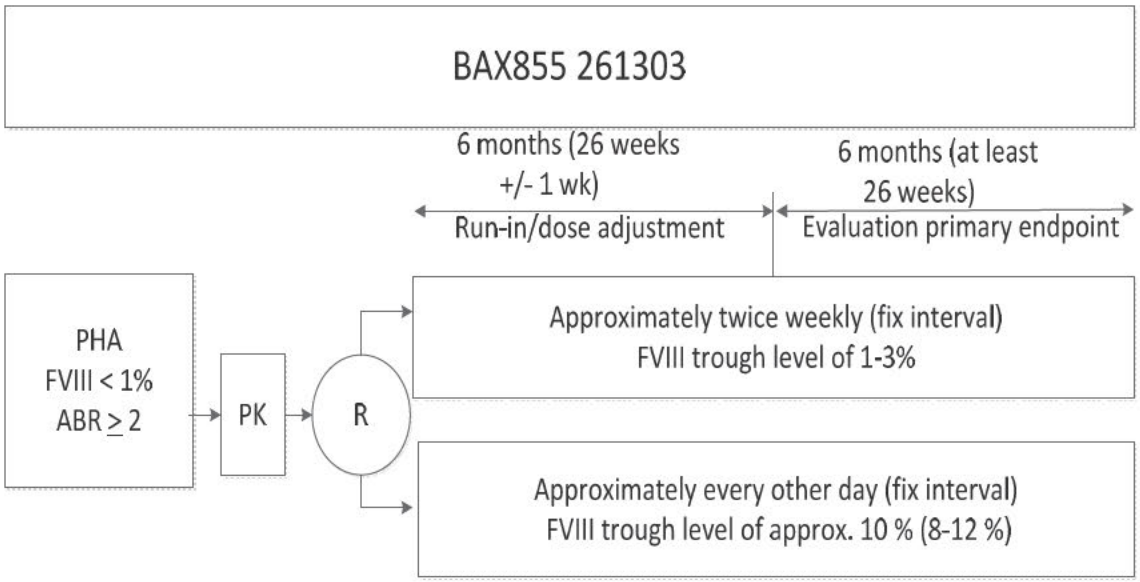
20. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

21. SUPPLEMENTS

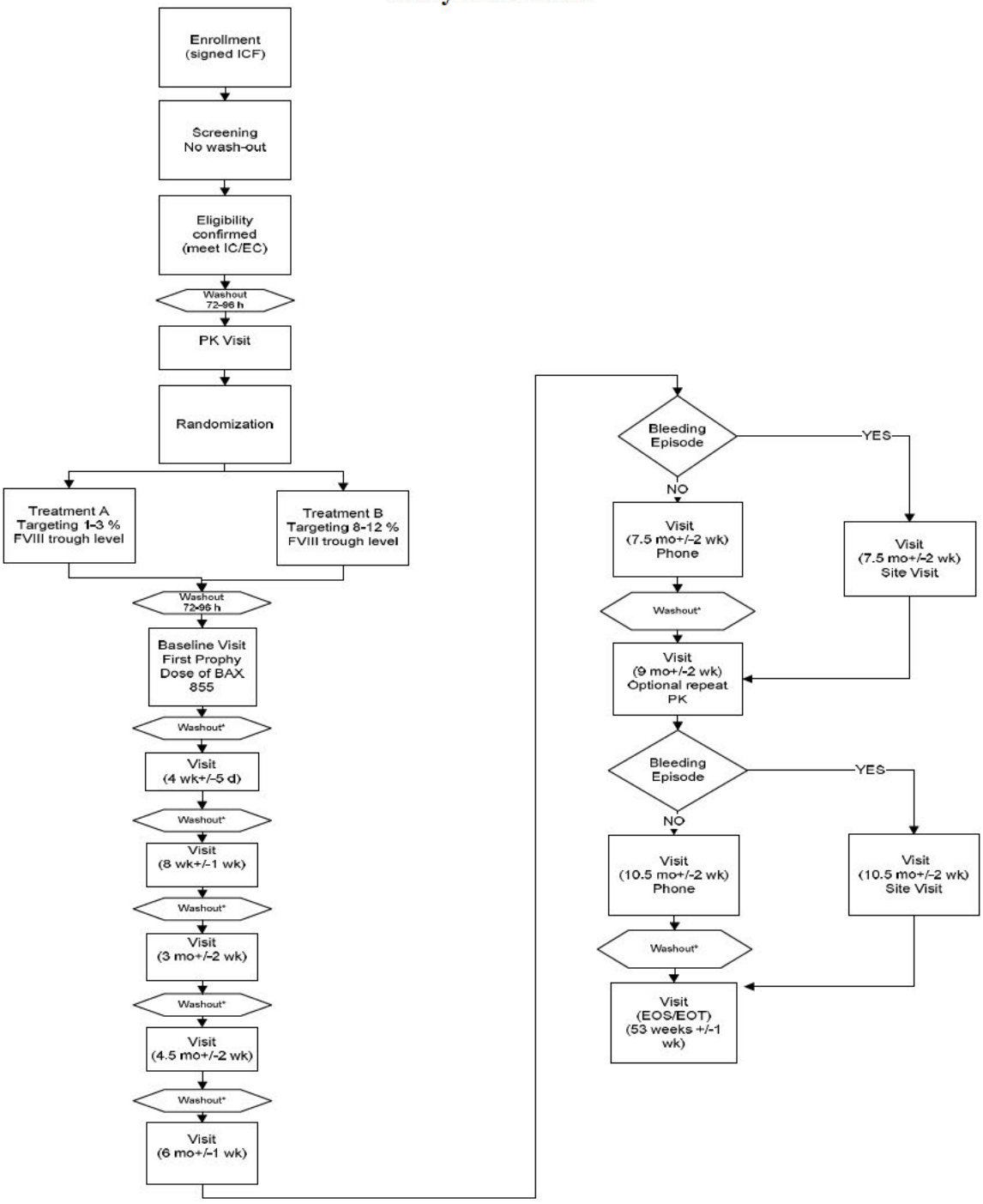
21.1 Study Flow Charts

Figure 1
Study Design for Baxalta Clinical Study 261303



ABR = Annualized bleeding rate
FVIII = Factor VIII
PHA = Patient with severe Hemophilia A
PK = Assessment of individual PK parameters
R = Randomization

Figure 2
Study Flow Chart



* Washout period: Consistent with the infusion interval according to the treatment regimen provided to the subject and immediately before the next planned regular prophylactic infusion.

21.2 Detailed Flow Diagram of Study Procedures

Before **any** study procedures are performed, informed consent must be obtained from each subject.

Screening Visit

The screening procedures differ according to whether the subject is **transitioning from a previous BAX 855 study** (see Section A) or is newly recruited (see Section B). If the sponsor decides a transitioning subject requires a PK Assessment, then from the screening visit onwards procedures are identical to those for newly recruited subjects. If no PK Assessment is required, the next visit for transitioning subjects is the Baseline Visit once randomization is performed.
 	
Evaluations must be completed within 56 days of the screening visit.
 	
No washout is required but whenever possible the screening visit should be scheduled shortly before the next scheduled prophylactic infusion when baseline FVIII trough levels are reached in case the subject receives prophylactic treatment.
 	
A: Subjects transitioning from other BAX 855 studies
 	
The screening visit coincides with the end of study visit of the previous BAX 855 study; the subject must not be actively bleeding. If applicable, BAX 855 will be administered for IR determination based on the protocol of the previous study.
 	
Informed consent must be obtained at enrollment at the latest (prior to any study-specific procedure); to give the subject sufficient time to review the ICF, this document should preferably be provided prior to the end of study visit of the previous study.
 	
The relevant data obtained at the end of study visit of the previous BAX 855 study will be transcribed to the screening visit eCRF of this PK-guided dosing study, and where possible, duplication of blood draws or evaluations will be avoided.
 	
<u>The following procedures will be performed:</u>
 	
Clinical Assessments:
• Assessment of inclusion/exclusion criteria
• PROs (or can be done at Baseline visit) should be determined prior to any other study specific procedures:
  o Haemo-SYM questionnaire
  o EQ-5D
  o SF-36
  o Physical activity questionnaire
  o Health Resource Use
 	
Laboratory Assessments:
Blood will be drawn for the following additional assessments:
• Screening tests:
  o CD4 count in subjects who are HIV positive
  o Viral serology (if any positive, test to be confirmed with a second sample) :
  ▪ HIV: HIV-1 and HIV-2 Ab
  ▪ HBV: HBsAg, HBsAb, HBcAb
  ▪ HCV: HCVAb (PCR to be performed if positive)
• Pregnancy test, if applicable

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

- Medical history
- Medication history
- Concomitant medications
- Non-drug therapies
- Physical examination (including assessment of target joints)
- Vital signs (body temperature [°C], respiratory rate [breaths/min], pulse rate [beats/min], and supine systolic and diastolic blood pressure [mmHg]).
- Laboratory Data:
    - FVIII/VWF/TGA assays:
        - FVIII activity (activated partial thromboplastin-based 1-stage clotting assay and chromogenic assay)
        - FVIII antigen
        - VWF antigen
        - TGA, if not available from previous study, an additional blood sample has to be drawn for TGA testing
    - Immunogenicity tests:
        - Inhibitory antibodies to FVIII (Nijmegen assay)
        - Binding antibodies (IgG and IgM) to FVIII, BAX 855, and PEG
        - Anti-CHO antibodies
    - Hematology, clinical chemistry, and lipids
    - Gene mutation and HLA genotype if not available
    - Blood type (A, B, AB or O) if historical data not available

Subject diary:

- Hand out subject diary and provide training to subject

Other procedures:

- Dispense IP:
    - A sufficient quantity of IP of study 261303 will be dispensed to cover the period until the PK Assessment / Baseline visit (as applicable)

B: Newly recruited subjects

- Ensure informed consent has been obtained
- Medical history
- Hemophilia history, including:
    - Confirmation of diagnosis and severity
    - Family history of hemophilia
    - Documentation of mutation, if known
    - The presence of any target joints will be documented. A target joint is defined as any single joint (ankles, knees, hips, or elbows) with ≥4 spontaneous bleeding episodes in any consecutive 6 month period.
    - Documentation of all FVIII replacement therapies used within the last year, including:
        - Date of last FVIII infusion prior to screening visit, type of FVIII product, dose infused and reason for administration
        - FVIII regimen (prophylaxis or on-demand)
        - Product name (or IP name and manufacturer, if applicable)
        - Dose (for prophylaxis, if applicable, and for treatment of bleeding episodes)

        - Frequency of administration (for prophylaxis)
        - Estimate of average number of infusions for each bleeding episode and usual response
    - Assessment of subject's ABR based on documented and treated bleeding episodes within 12 months before enrolment, based on subject's medical records.
- Concomitant medications for the last 30 days, and any prior history of use of any pegylated medication (e.g., PEG-interferon) at any time in the past, including treatment indication, date of last administration, and duration of treatment(s), if known
- Non-drug therapies for the last 30 days
- Physical examination, including height and weight
- Karnofsky performance score
- Vital signs (body temperature [°C], respiratory rate [breaths/min], pulse rate [beats/min], and supine systolic and diastolic blood pressure [mmHg]).
- PROs (or can be done at Baseline visit) should be determined before any other study specific procedures are performed:
    - Haemo-SYM questionnaire
    - EQ-5D
    - SF-36
    - Physical activity questionnaire
    - Health Resource Use

Laboratory Assessments:
Blood will be drawn for the following assessments:

- Screening tests:
    - CD4 count in subjects who are HIV positive
    - Viral serology (if any positive, test to be confirmed with a second sample) :
        - HIV: HIV-1 and HIV-2 Ab
        - HBV: HBsAg, HBsAb, HBcAb
        - HCV: HCVAb (PCR to be performed if positive)
    - Genetics (FVIII gene mutation analysis) and HLA-genotype if historical data not available
    - Blood type (A, B, AB or O) if historical data not available
- FVIII/VWF/TGA assays:
    - FVIII activity (activated partial thromboplastin-based 1-stage clotting assay and chromogenic assay)
    - FVIII antigen
    - VWF antigen
    - TGA
- Immunogenicity tests:
    - Inhibitory antibodies to FVIII (Nijmegen assay)
    - Binding antibodies (IgG and IgM) to FVIII, BAX 855, and PEG
    - Anti-CHO antibodies
- Hematology, clinical chemistry, and lipids
- Pregnancy test, if applicable

Subject diary:

- Hand out subject diary and provide training to subject

PK Assessment

Subjects transitioning from another BAX 855 study who have already had a PK assessment may have to repeat the PK assessment based on the sponsor's evaluation. The PK assessment has to be performed after a washout period of at least 72-96 h depending on the FVIII concentrate used and the subject should not be actively bleeding.

Blood sampling after infusion of BAX 855 for PK assessments will be performed over a 4-day period.

- Review and discuss subject diary

At the **pre-infusion** timepoint, the following assessments will be carried out:

- Laboratory Assessments (within 30 minutes of start of infusion):
  - FVIII assays
  - VWF antigen
  - TGA
- Vital signs (within 15 minutes of start of infusion)

Infusion:

- Infusion of 60 ±5 IU/kg BAX 855

Post-infusion:

- Laboratory Assessments:
  - FVIII assays and TGA at the post-infusion timepoints, 15-30 min, 3 ±0.5 h, 8 ±0.5 h, 24 ±2 h , 48 ±4 h, 72 ±4 h and 96 ±4 h

At 30 ±5 min post-infusion:

- Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure)

Throughout the visit, the following assessments will be carried out:

- Physical examination
- Adverse events
- Concomitant medications and non-drug therapies

Randomization

Once the FVIII activity results are available, the PK parameters calculated, subjects will be randomized to one of the treatment arms.

Baseline Visit

The washout periods are at least 72–96 h and the subject must not be actively bleeding. Evaluations must be completed within 56 days of the PK Assessment. Whenever possible the PRO questionnaires should be completed before all other study specific procedures are started.

At the **pre-infusion** timepoint, the following assessments will be carried out:

- PROs (if not done at Screening visit):
  - Haemo-SYM questionnaire
  - EQ-5D
  - SF-36
  - Physical Activity
  - Health Resource Use
- Review and discuss subject diary
- Physical examination, including body weight, and assessment of target joints
- Vital signs (within 15 minutes of start of infusion)
- Laboratory Assessments (within 30 minutes before start of infusion):
  - Hematology, clinical chemistry, and lipids
  - FVIII, VWF Ag and TGA assays
  - Immunogenicity tests:
    - Inhibitory antibodies to FVIII (Nijmegen assay)
    - Binding antibodies (IgG and IgM) to FVIII, BAX 855, and PEG
    - Anti-CHO antibodies
  - Additional blood draw for further exploratory testing (i.e., additional biomarkers for hemophilia)

Infusion:

- Infusion of PK-guided dose of BAX 855

Post-infusion:

At 15-30 min post-infusion:

- Laboratory Assessments:
  - FVIII and TGA assays

At 30 ±5 min post infusion:

- Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure)

Other procedures:

- **Dispense IP**
- HJHS joint score
- X-ray of impaired joint, if applicable (if not already available and not older than 12 months), can also be performed at visit Week 4 ±5 days.

Throughout the visit, the following assessments will be carried out:

- Adverse events
- Concomitant medications and non-drug therapies

Visits at Study Site:

3 months ± 2 weeks

6 months ± 1 week (26 ±1 week)

For the procedures **at 4 weeks ±5 days, 8 weeks ±1 week** and **4.5 months ±2 weeks**, see next section.

The procedures listed here will also be carried out at **7.5 months ±2 weeks** and **10.5 months ±2 weeks if subject has bleeding and attends site rather than having a phone visit.**

The washout periods are consistent with the infusion interval according to the treatment regimen provided to the subject and immediately before the next planned regular prophylactic infusion.

The subject must not be actively bleeding.

Before any other study-specific procedures are carried out:

- PROs at 6 month visit
  - Haemo-SYM questionnaire
  - EQ-5D
  - SF-36
  - Physical Activity
  - Health Resource Use
- EQ-5D, Patient Activity Level, and Health Resource Use at each visit
- Physical examination, including body weight, and assessment of target joints
- Review and discuss subject diary, including assessment of bleeding episodes and their treatment, and type and duration of physical activity
- Re-evaluation of PK regimen based on pre-dose FVIII trough level from previous visit, change in body weight. Note: before any dose adjustments are performed an additional visit should be scheduled within 14 days after receipt of the FVIII activity result to reassess trough levels.

At the **pre-infusion** timepoint:

- Vital signs (within 15 minutes of start of infusion)
- Laboratory Assessments (within 30 minutes before start of infusion):
  - Hematology, clinical chemistry, and lipids (clinical chemistry and lipids are not applicable at study visits 7.5 months ±2 weeks and 10.5 months ±2 weeks)
  - FVIII, VWF Ag and TGA assays
  - Immunogenicity tests:
    - Inhibitory antibodies to FVIII (Nijmegen assay)
    - Binding antibodies (IgG and IgM) to FVIII, BAX 855, and PEG
    - Anti-CHO antibodies
  - Additional blood draw for further exploratory testing

Infusion:

- Infusion of PK-guided prophylactic dose of BAX 855

Post-infusion:

At 15-30 min post-infusion:

- FVIII and TGA assays

At 30 ±5 min post-infusion:

- Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure)

Dispense IP

Throughout the visit, the following assessments will be carried out:

- Adverse events
- Concomitant medications and non-drug therapies

Visits at Study Site: **4 weeks ±5 days** **8 weeks ±1 week** **4.5 months ±2 weeks** **Dose Readjustment Visit** **Visits following dose adjustment**
The washout periods are consistent with the infusion interval according to the treatment regimen provided to the subject and immediately before the next planned regular prophylactic infusion. The subject must not be actively bleeding. These procedures will also be followed if a subject attends an additional visit to check trough FVIII levels prior to any dose readjustment. **Before** any other study-specific procedures are carried out: • EQ-5D, Patient Activity Level and Health Resource Use • Review and discuss subject diary, including assessment of bleeding episodes and their treatment and type and duration of physical activity • Re-evaluation of FVIII regimen based on pre-dose FVIII trough level from previous visit, if applicable, change in body weight. Note: before any dose adjustments are performed an additional visit should be scheduled in 14 days to reassess trough levels At the **pre-infusion** timepoint, the following assessments will be carried out: • Vital signs (within 15 minutes of start of infusion) • Laboratory Assessments: o FVIII, VWF Ag and TGA assays (within 30 minutes of start of infusion) • Immunogenicity tests (within 30 minutes of start of infusion): o Inhibitory antibodies to FVIII (Nijmegen assay) o Binding antibodies (IgG and IgM) to FVIII, BAX 855, and PEG o Anti-CHO antibodies **Infusion**: • Infusion of PK-guided dose of BAX 855 **FVIII trough level measurement following dose adjustment** Those subjects who had dose adjustment will undergo a repeat FVIII trough level measurement approximately 2 weeks following their dose adjustment. The measurement should be performed immediately prior to their next scheduled prophylactic infusion: Only the following assessment will be performed: • Laboratory Assessments: o FVIII, VWF Ag and TGA assays (within 30 minutes of start of infusion) **Throughout the visit**, the following assessments will be carried out: • Adverse events • Concomitant medications and non-drug therapies **IP dispense**

Phone Visits:

7.5 months ±2 weeks

10.5 months ±2 weeks

If subjects experienced bleeding episodes between the last visit and visit 7.5 months ±2 weeks and 10.5 months ±2 weeks, respectively, they must visit the site rather than having a phone visit.

The subject will be contacted by phone and will be asked about the following:

- Review and discuss subject diary
- Bleeding episodes and their treatment
- Adverse events
- Concomitant medications and non-drug therapies

In case of bleeding episodes the laboratory assessment as described for study visit Month 3 ±2 weeks and Month 6 ±1 week may be performed.

Visit at Study Site:

9 months ±2 weeks

The washout periods are consistent with the infusion interval according to the treatment regimen provided to the subject and immediately before the next planned regular prophylactic infusion.

The subject must not be actively bleeding.

Before any other study-specific procedures are carried out:

- EQ-5D, Patient Activity Level, and Health Resource Use
- Review and discuss subject diary, including assessment of bleeding episodes and their treatment and type and duration of physical activity
- Physical examination, including body weight, and Assessment of target joints

At the **pre-infusion** timepoint, the following assessments will be carried out:

- Vital signs (within 15 minutes of start of infusion)
- Laboratory Assessments (within 30 minutes of start of infusion):
  - FVIII, VWF Ag and TGA assays
  - Hematology, clinical chemistry, and lipids
- Immunogenicity tests (within 30 minutes of start of infusion):
  - Inhibitory antibodies to FVIII (Nijmegen assay)
  - Binding antibodies (IgG and IgM) to FVIII, BAX 855, and PEG
  - Anti-CHO antibodies
- Additional blood draw for further exploratory testing

Infusion:

- Infusion of 60 ±5 IU/kg BAX 855, in case of optional PK, OR
- Infusion of prophylactic dose of BAX 855, in case of IR only

Post-infusion:

- Laboratory Assessments:
  - FVIII assays and TGA at 15-30 minutes post-infusion (IR only)
  - Optional timepoints in case of PK: 3 ±0.5 h, 8 ±0.5 h, 24 ±2 h , 48 ±4 h, 72 ±4 h and 96 ±4 h
- At 30 ±5 min post-infusion: Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure)

Dispense IP

Throughout the visit, the following assessments will be carried out:

- Adverse events
- Concomitant medications and non-drug therapies

Completion/Termination Visit:

at 12 months ± 1 week (53 [±1] weeks)

When planning the Completion/Termination Visit, it must be ensured that the second 6-month study period will consist of a minimum of 26 weeks and that the subject will have received his PK-tailored dosing regimen for at least 52 weeks.

The washout periods are consistent with the infusion interval according to the treatment regimen provided to the subject and immediately before the next planned regular prophylactic infusion.

The subject must not be actively bleeding.

Before any other study-specific procedures are carried out:

- PROs:
  - Haemo-SYM questionnaire
  - SF-36
  - EQ-5D
  - Physical Activity
  - Health Resource Use
- Return of subject diary and review and discuss entries with subject, including assessment of bleeding episodes and their treatment and type and duration of physical activity
- Physical examination, including body weight; Assessment of target joints; HJHS joint score

At the **pre-infusion** timepoint, the following assessments will be carried out:

- Vital signs (within 15 minutes of start of infusion)
- Laboratory Assessments:
  - FVIII, VWF Ag and TGA assays (within 30 minutes of start of infusion)
  - Hematology, clinical chemistry, and lipids
- Immunogenicity tests (within 30 minutes of start of infusion):
  - Inhibitory antibodies to FVIII (Nijmegen assay)
  - Binding antibodies (IgG and IgM) to FVIII, BAX 855, and PEG
  - Anti-CHO antibodies
- Additional blood draw for further exploratory testing

Infusion:

- Infusion of PK-guided prophylactic dose of BAX 855

Post-infusion:

- Laboratory Assessments:
  - FVIII assays and TGA (15-30 minutes after start of infusion)

At 30 ±5 min post-infusion:

- Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure)

Throughout the visit, the following assessments will be carried out:

- Adverse events
- Concomitant medications and non-drug therapies

21.3 Schedule of Study Procedures and Assessments

Procedures/ Assessments	**Screening Visit**	**PK Assessment[a]** Pre infusion, 15-30 min, 3 ±0.5 h, 8 ±0.5 h, 24 ±2 h. 48 ±4 h, 72 ±4 h & 96 ±4 h Post- Infusion	**Baseline Visit**	**Study Visits**								**Completion/ Termination Visit[c] 12 Mo (53 ±1 Wk)**
				Visit 4Wk ±5d	**Visit 8Wk ±1Wk**	**Visit 3 Mo ±2Wk**	**Visit 4.5 Mo ±2Wk**	**Visit 6 Mo ±1Wk (26 ±1Wk)**	**Phone Visit 7.5 Mo ±2Wk[b]**	**Visit 9 Mo ±2Wk + optional PK**	**Phone Visit 10.5 Mo ±2wk[b]**	
Washout	N/A	72-96 h		Consistent with the infusion interval according to the treatment regimen provided to the subject and immediately before the next planned regular prophylactic infusion.								
Informed consent[d]	X											
Eligibility criteria	X											
Medical and medication history[e]	X*											
Concomitant medications[f]	X*	X	X	X	X	X	X	X	X	X	X	X
Non-drug therapies[f]	X*	X	X	X	X	X	X	X	X	X	X	X
Physical exam[g]	X*	X	X			X		X	(X)[b]	X	(X)[b]	X
Vital signs[h]	X*	X	X	X	X	X	X	X	(X)[b]	X	(X)[b]	X
Adverse events[f]	*	X	X	X	X	X	X	X	X	X	X	X
Bleeding episodes and their treatment[f,i]	*			X	X	X	X	X	X	X	X	X
Assessment of target joints[j]	X		X			X		X	(X)	X	(X)	X
Joint score (HJHS)			X									X
X-ray of impaired joint			X[k]	(X)[k]								
Subject diary[l]	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments[m]	X*	X	X	X	X	X	X	X	(X)[b]	X	(X)[b]	X
IP treatment[n]		X	X	X	X	X	X	X	(X)[b]	X	(X)[b]	X
IP dispense[o]	X[n]	(X)	X	X	X	X	X	X		X		

Procedures/ Assessments	**Screening Visit**	**PK Assessment[a]** Pre infusion, 15-30 min, 3 ±0.5 h, 8 ±0.5 h, 24 ±2 h. 48 ±4 h, 72 ±4 h & 96 ±4 h Post- Infusion	**Baseline Visit**	**Study Visits**								**Completion/ Termination Visit[c] 12 Mo (53 ±1 Wk)**
				Visit 4Wk ±5d	**Visit 8Wk ±1Wk**	**Visit 3 Mo ±2Wk**	**Visit 4.5 Mo ±2Wk**	**Visit 6 Mo ±1Wk (26 ±1Wk)**	**Phone Visit 7.5 Mo ±2Wk[b]**	**Visit 9 Mo ±2Wk + optional PK**	**Phone Visit 10.5 Mo ±2wk[b]**	
Washout	N/A	72-96 h		Consistent with the infusion interval according to the treatment regimen provided to the subject and immediately before the next planned regular prophylactic infusion.								
Re-evaluation of PK regimen/dose adjustments[p]				X	X	X	X	X	(X)[b]	(X)	(X)[b]	
PROs[q]	(X)[r]		(X)	(X)[r]	(X)[r]	(X)[r]	(X)[r]	X	(X)[r]	(X)[r]	(X)[r]	X

* The screening visit coincides with the end of study visit of the previous BAX 855 study. The procedures/assessments marked with an asterisk (*) will be transcribed from the end of study visit of the previous BAX 855 study.

a Subjects transitioning from another BAX 855 study may have to repeat the PK assessment if evaluated to be necessary by the sponsor. The washout period prior to the initial PK determination is 72-96 hours, depending on the FVIII concentrate. An optional PK will also be performed at the 9-month visit (steady state PK) with the same post-infusion sampling timepoints.

b If a subject has a bleeding episode, instead of a phone visit the subject must attend a site visit to assess FVIII trough levels and IR and re-evaluate the PK-guided regimen (see Figure 2). In these cases the subject will undergo all planned assessments for a study visit, including assessment of vital signs, physical examination, and all laboratory assessments excluding clinical chemistry and the lipid panel.

c Including subjects who withdraw or discontinue. When planning the Completion/Termination Visit, it must be ensured that the second 6-month study period will consist of a minimum of 26 weeks and that the subject will have received his PK-tailored dosing regimen for at least 52 weeks.

d Occurs at enrollment (prior to any study-specific procedure).

e Medical history to include hemophilia history (confirmation of diagnosis & severity; family history of hemophilia; documentation of a mutation, if known; presence of any target joints; and historical ABR, blood group if available). Medication history to include documentation of all FVIII replacement therapies used within the last year, any prior history of use of any pegylated medication (e.g., PEG-interferon) at any time in the past, and other medications in the last 30 days.

f Indicates that adverse events, concomitant medications, non-drug therapies, bleeding episodes and their treatment as well as the physical activity levels 8 hours prior to the occurrence of bleeding will be continuously monitored but specifically discussed and reviewed at these timepoints.

g Includes height and weight at screening, weight at the pre-infusion assessments, and Karnofsky performance score at screening.

h Pulse, respiration, supine blood pressure, and temperature to be assessed within 15 minutes prior to start of infusion and 30 ±5 minutes following infusion.

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[i] The physical activity level in the 8 hours before the start of the bleeding episode should also be recorded.
[j] A target joint is defined as one in which there have been ≥4 bleeds in any consecutive 6-month period.
[k] At baseline or Week 4 ±5 days. If an X-ray of an impaired joint evaluated as part of the HJHS is already available and not older than 12 months, it does not have to be repeated.
[l] The subject diary will be handed out at screening and training will be provided at the subsequent visits and the entries are reviewed and discussed with subject. It will be used to document bleeds, any physical activity in the 8 hours before the bleed (see Section 8.2), treatment administered and response to BAX 855, prophylactic infusions, untoward events, concomitant medications, PROs and health resource use data, if applicable.
[m] For laboratory assessments, See Section 21.4.
[n] BAX 855 is administered in the clinic at the visits shown. At the PK assessment(s), a set dose of 60 ±5 IU/kg BAX 855 is used; in all other cases, including the determination of IRs, the dose is PK-guided according to the allocated regimen.
[o] Transitioning subjects will receive IP of study 261303 as of the screening visit. Newly recruited subjects will continue with their previous treatment regimen until the first prophylactic PK-guided infusion at baseline and the infusion for PK determination.
[p] In the first 6-month period, adjustments can be made based on PK and FVIII trough levels from previous study visits. Dose adjustments in second 6-month period are only permitted when FVIII trough levels are outside of the target window. Adjustments should be based on PK, pre-dose FVIII trough level from previous visit, any change in body weight, and assessment of any spontaneous bleeds. Before any dose adjustments are performed an additional visit should be scheduled within 14 days after receipt of FVIII activity results. Details of dose adjustments will be provided in a separate document.
[q] PROs include: Haemo-SYM Questionnaire, EQ-5D questionnaire, Short-Form 36 (SF-36), Physical Activity, and Health Resource Use; PROs can be done either at screening visit or baseline visit. Should always be completed before any study visit specific procedure.
[r] EQ-5D, Patient Activity Level and Health Resource Use will be determined at each study visit.

21.4 Clinical Laboratory Assessments

Procedures/ Assessments[a]	Screening Visit	PK Assessment[b]	Baseline Visit	Study Visits[c]								
		Pre Infusion, 15-30 Min, 3 ±0.5 h, 8 ±0.5 h, 24 ±2 h, 48 ±4 h, 72 ±4 h & 96 ±4 h Post-Infusion		Visit 4Wk ±5d	Visit 8Wk ±1Wk	Visit 3 Mo ±2Wk	Visit 4.5 Mo ±2Wk	Visit 6 Mo ±1Wk (26 ±1 Wk)	Visit 7.5 Mo ±2Wk[q]	Visit 9 Mo ±2Wk +optional PK	Visit 10.5 Mo ±2Wk[q]	Completion/ Termination Visit[d] 12 Mo (53 ±1Wk)
Washout for FVIII and immunogenicity testing	None	72-96 h		Consistent with the infusion interval according to the treatment regimen provided to the subject and immediately before the next planned regular prophylactic infusion.								
CD4 count[e]	X											
Genetics and HLA-genotype[f]	X											
Viral serology[g]	X											
Blood type[h]	X											
Pregnancy Test (if applicable)[i]	X											
FVIII and VWF:Ag assays[j]	X	X	X^k	X	X	X^k	X	X^k	(X^k)	X^k	(X^k)	X^k
Immunogenicity[l]	X		X	X	X	X	X	X	(X)	X	(X)	X
Hematology[m]	X		X			X		X	(X)	X	(X)	X
Clinical chemistry and lipid panel[n]	X		X			X		X		X		X
TGA[o]	X	X	X	X	X	X	X	X	(X)	X	(X)	X

Procedures/ Assessments[a]	**Screening Visit**	**PK Assessment**[b] Pre Infusion, 15-30 Min, 3 ±0.5 h, 8 ±0.5 h, 24 ±2 h, 48 ±4 h, 72 ±4 h & 96 ±4 h Post-Infusion	**Baseline Visit**	**Study Visits**[c] **Visit 4Wk ±5d**	**Visit 8Wk ±1Wk**	**Visit 3 Mo ±2Wk**	**Visit 4.5 Mo ±2Wk**	**Visit 6 Mo ±1Wk (26 ±1 Wk)**	**Visit 7.5 Mo ±2Wk**[q]	**Visit 9 Mo ±2Wk +optional PK**	**Visit 10.5 Mo ±2Wk**[q]	**Completion/ Termination Visit**[d] **12 Mo (53 ±1Wk)**
Washout for FVIII and immunogenicity testing	None	72-96 h		Consistent with the infusion interval according to the treatment regimen provided to the subject and immediately before the next planned regular prophylactic infusion.								
Additional blood draw for further exploratory testing[p]			X			X		X		X		X

[a] At all assessments subjects must not be actively bleeding. In addition to the assessments shown, clinical laboratory tests should be performed whenever clinically indicated.

[b] Subjects transitioning from another BAX 855 study may have to repeat the initial PK assessment if evaluated to be necessary by the sponsor. The washout period prior to the PK determination is 72-96 hours, depending on the FVIII concentrate. An optional PK will also be performed at the 9-month visit (steady state PK) with the same post-infusion sampling timepoints. The washout period prior to the optional repeat PK will be consistent with the subject's individual dosing interval.

[c] If a subject has a bleeding episode since the last visit before the 7.5 month ±2 week or 10.5 month ±2 week visits, instead of a phone visit the subject must attend a site visit to assess FVIII trough levels and IR and re-evaluate the PK-guided regimen. In these cases, the subject will undergo all assessments as listed for the 3 and 6 month ±2 week visits.

[d] Including subjects who withdraw or discontinue. When planning the Completion/Termination Visit it must be ensured that the second 6-month study period will consist of a minimum of 26 weeks and that the subject will have received his PK-tailored dosing regimen for at least 52 weeks.

[e] CD4 count is analyzed in HIV positive subjects only to determine eligibility.

[f] If results of FVIII gene mutation analysis and HLA genotype are already available at the study site, they will be provided to the sponsor and an additional analysis will not be required.

[g] Viral serology includes: HIV-1, HIV-2, HBcAb, HBsAb, HBsAg, HCVAb. Any HCV positive sample will be tested by PCR for viral titer.

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

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[i] Pregnancy test as appropriate (serum pregnancy test in females of child-bearing potential if no urine sample is available). The pregnancy test might be repeated during the study in countries where mandated by national law.

[j] Factor VIII assays include: 1-stage clotting FVIII activity, FVIII chromogenic activity, and FVIII antigen. For assessment of trough levels, a blood sample will be taken within 30 minutes before the IP infusion. VWF antigen level will only be determined pre-infusion at each study visit.

[k] For assessment of FVIII IR, in addition to the pre-infusion sample a second sample will be taken 15-30 minutes after IP infusion.

[l] 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 will be measured. Blood draws have to be performed within 30 min before the IP infusion.

[m] Hematology assessments include: hemoglobin, hematocrit, red blood cell count, and white blood cell count with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, and neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and platelet count. Samples should be taken within 30 minutes before the start of IP infusion.

[n] Clinical chemistry assessments include: sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, and glucose. Lipid panel includes cholesterol, very low density lipoprotein (VLDL), low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides. Samples should be taken within 30 minutes before the start of IP infusion.

[o] TGA parameters are lag time, time to peak thrombin generation, peak thrombin generation, and endogenous thrombin potential [ETP] Samples will be taken together with blood samples for FVIII activity and antigen determination.

[p] Blood draws for additional exploratory testing (i.e., biomarkers for hemophilia) will be drawn pre-infusion and early in the morning if feasible, otherwise at the same timepoint at each study visit.

[q] Only applicable for subjects who experience bleeding episodes since the previous study visit who have to perform a study site visit.

22. PERIOPERATIVE MANAGEMENT

22.1 Types of Interventions

22.1.1 Major Surgeries

Major surgeries involve surgeries which require moderate or deep sedation, general anesthesia, or major conduction blockade for patient comfort. It generally refers to major orthopedic (e.g., joint replacement), major abdominal, intracranial, cardiovascular, spinal and any other surgery which has a significant risk of large volume blood loss or blood loss into a confined anatomical space. Extractions of several teeth or extraction of the third molar are generally considered as major. In children it may include adeno-tonsillectomy. Examples include:

- bone fixation for fractures
- hip and knee replacements (arthroplasties)
- arthrodeses (joint fusions)
- open synovectomies
- osteotomies
- liver biopsy
- pseudotumor removal, hepatectomy, colectomy, tumor removal,
- hardware removal (plates, intramedullary nails),etc.

Major surgeries/interventions are expected to require clinical surveillance or hospital treatment >3 days after the surgery/intervention.

22.1.2 Minor Surgeries

Minor surgeries comprise surgeries which can be safely and comfortably performed on a patient who has received local or topical anesthesia, without more than minimal preoperative medication or minimal intraoperative sedation. The likelihood of complications requiring hospitalization or prolonged hospitalization is remote. It refers to interventions such as:

- removal of skin lesions
- arthroscopy and arthroscopic procedures, like synovectomies
- minor dental procedures or dental extractions (except extraction of several teeth or third molar extraction)
- placement and/or removal of central venous catheters
- synoviorthesis and arthrocentesis
- nerve release
- removal of osteophytes and small cysts

Minor surgeries/interventions are expected to require clinical surveillance or hospital treatment ≤ 3 days after the surgery/intervention.

22.2 Dosing Schedule and Requirements for Major Surgery

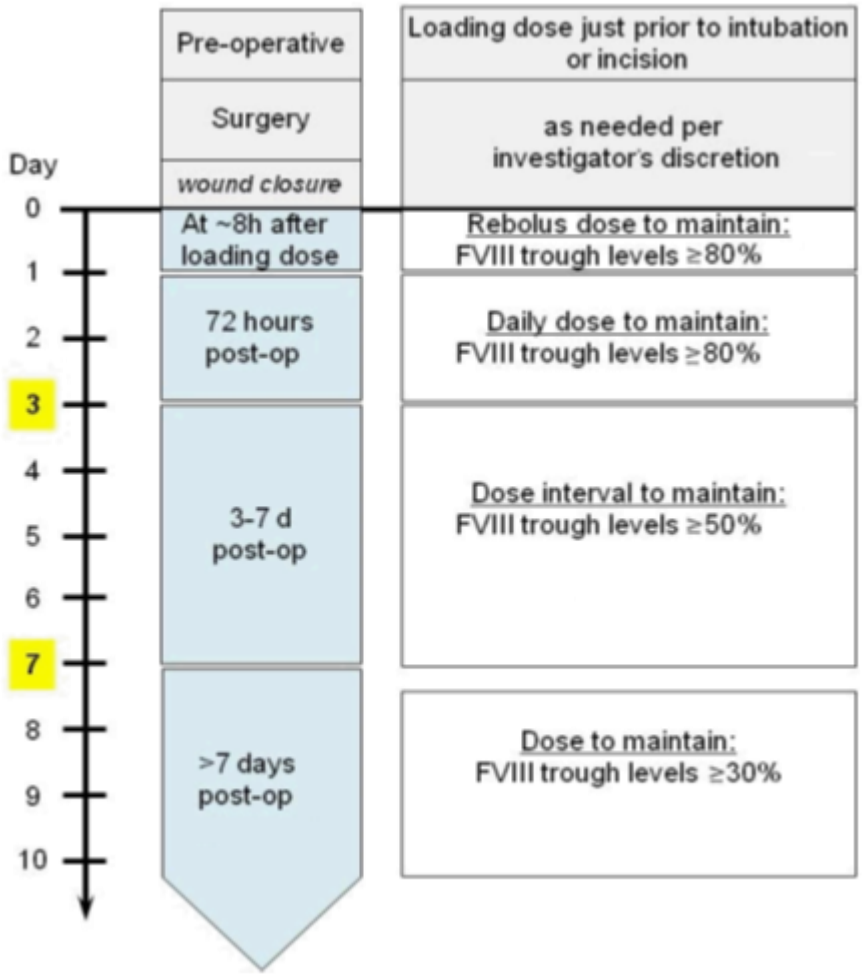
A detailed list of procedures is shown in Table 8, and a summary schedule of assessments and laboratory sampling in Table 9.

22.3 FVIII Substitution Plan

Based on the category (minor or major) and type of surgery, the investigator must outline the expected FVIII substitution plan with target peak and trough levels covering the surgical, dental or invasive procedure until expected wound healing. The FVIII levels measured intra/postoperatively will be compared with the FVIII substitution plan. Slight deviations from the predefined substitution plan are allowed based on investigators clinical judgment and available laboratory FVIII data.

Figure 3 is a visualization of timing and target FVIII levels for major surgery.

Figure 3
Dosing Recommendations for Major Surgeries



22.3.1 General

The dose and frequency of BAX 855 administered will be individualized based on the subject's IR and half-life, if available, and the required FVIII target levels.

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

Required units (IU) =
body weight (kg) x desired FVIII rise (IU/dL) x {reciprocal of IR} (IU/kg)/(IU/dL)

Example: In case of an IR of 2.0 [IU/dL]/[IU/kg], the required units would be calculated using the following formula:

body weight (kg) x desired FVIII rise (IU/dL) x 0.5 (IU/kg)/(IU/dL)

If at any time during the perioperative period, a subject does not respond to BAX 855 therapy as anticipated either by the operating surgeon or hemophilia physician providing postoperative care, blood samples will be drawn for the determination of FVIII activity levels and inhibitory antibodies to FVIII. In the event of unexplained, excessive bleeding, the subject will be treated by whatever means necessary until adequate hemostasis is achieved. The use of adjunct antifibrinolytic therapy such as e.g., tranexamic acid is allowed if clinically indicated by the investigator and/or according to the standard of care of the subject's institution.

22.3.2 Preoperative and Loading Dose

The subject will receive a loading dose calculated according to the formula described above in order to maintain a minimum target FVIII level as required by the category and type of surgery. The recommended loading dose will be calculated by the investigator.

The initial loading dose will be administered within 60 minutes prior to surgery (prior to incision/intubation). Vials of varying potencies may be used to ensure adequate dosing. A blood sample for post infusion FVIII at 15 ±5 minutes after completion of the initial loading dose will be drawn to ensure that the required FVIII levels have been obtained. Also, a pre-infusion blood sample may be drawn within 30 minutes prior to the loading dose. Activated partial thromboplastin time (aPTT) will also be determined from the post infusion blood sample.

In case of major surgery, FVIII target levels should be 80-100% of normal, in case of minor surgery FVIII levels should be at 30-60%.

If the FVIII activity results are not available within a reasonable time period prior to the start of surgery, at least the post-infusion value of the aPTT must be obtained. The FVIII activity level following the loading dose must be obtained within 4 hours of infusion of BAX 855 and dose adjustments must be performed as needed.

The surgery may only start after normalization of the aPTT.

If the aPTT is not normalized or the desired FVIII activity is not attained, a supplemental loading dose(s) of BAX 855 can be given at the discretion of the investigator.

Subsequent infusions of BAX 855 should be preceded by measurement of residual FVIII levels and dose adjustments must be based on the most recent residual FVIII activity levels.

22.4 Postoperative Dosing

Major surgery

After the initial loading dose, an optional re-bolus sufficient to raise FVIII levels to the appropriate level as defined for the type of surgery may be administered after a blood sample for FVIII determination has been drawn and the required FVIII levels by the local laboratory have been determined.

Note:

A second FVIII activity level should be determined within preferably 6-8 h following major surgery and within 12 h at the latest, with dose adjustments as necessary on the day of surgery.

ALL subsequent infusions of BAX 855 should be preceded by measurement of residual FVIII levels and the dose adjusted as needed. Dosing adjustments based on aPTT values are not allowed.

Based on each individual PK parameter, i.e., IR and half-life, if available, it is recommended that the following FVIII trough levels should be targeted for major surgery:

- The first postoperative 72 hours (Day 1-Day 3): ≥80%
- Postoperative Day 4-Day 7: ≥50% (if not yet discharged)
- Postoperative Day 8 to discharge (if not yet discharged) including intensified treatment for rehabilitation, if applicable: it is recommended that the FVIII levels should not fall below 30% (left to the discretion of the investigator depending on the postoperative course)

General postoperative treatment recommendations:

- Treatment intervals should be tailored in order not to exceed supraphysiological peak FVIII levels of 180%. Therefore, the dose should be administered in 1-3 infusions over 24 hours, most commonly in 2 infusions.
- The dose may be increased to a maximum of 100 IU/kg, however, the peak level should not exceed 180%.

Any modifications of the FVIII replacement recommendations and the substitution plan that are deemed necessary during the postoperative period will be at the discretion of the investigator and will be documented on the eCRFs.

Beginning postoperative Day 1 (i.e., the day following the day of surgery) through discharge, subjects will have a BAX 855 pre-infusion (within 30 minutes) and after 15 ±5 minutes a post-infusion FVIII level measurement at least once per day in order to assess the adequacy of factor replacement therapy during the postoperative period. For consistency, it is recommended that the daily blood draws are performed at the same time of the day, e.g., morning blood draws. At a minimum, a blood sample for FVIII determination must be drawn prior to any supplemental unscheduled FVIII infusion. In order to ensure the timely availability of the results, FVIII levels will be determined at the local laboratory. A back-up sample should be drawn for FVIII measurement at the central laboratory.

Minor surgeries

Subjects undergoing minor surgery can be re-dosed postoperatively with BAX 855 at 8-24 hour intervals. Trough levels of FVIII should be kept at 30-60% of normal for the first 24 hours or longer as deemed necessary by the investigator. At least 1 postoperative dose should be given calculated based on the individual IR value determined prior to surgery. If the individual IR could not be not determined before surgery, the average IR value of 2.0 IU/dL: IU/kg for BAX 855 should be used. The investigator must outline the expected FVIII substitution plan with target peak and trough levels during and following the surgical procedure until expected wound healing. The FVIII levels measured intra/postoperatively will be compared with the FVIII substitution plan. Slight deviations from the predefined substitution plan are allowed based on investigators´ clinical judgment and available laboratory FVIII data.

In case the subject is hospitalized for more than 24 hours, daily pre- and post-infusion FVIII level determinations as described for major surgery have to be performed and the dose adjusted according to the residual FVIII levels. As with major surgeries, the target FVIII levels should preferably not exceed 180%, otherwise the frequency should be increased.

22.5 Efficacy assessment

22.5.1 Intra-, Post-, and Perioperative Hemostatic Efficacy

The hemostatic efficacy will be assessed at the end of surgery (Table 5), at postoperative day 1 (Table 6), and overall as a perioperative assessment (Table 7).

Table 5 **Intraoperative Efficacy Assessment Scale**		
	Prior to the discharge from the recovery room, the operating surgeon will assess the intraoperative hemostatic efficacy compared to that expected for the type of procedure performed in a non-hemophilic population	
Rating	**Criteria**	
Excellent	Intraoperative blood loss was less than or equal to that expected (≤100%)	
Good	Intraoperative blood loss was up to 50% more than expected (101-150%)	
Fair	Intraoperative blood loss was more than 50% of that expected (>150%)	
None	Uncontrolled hemorrhage that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy	

Table 6 **Postoperative Efficacy Assessment Scale (Postoperative Day 1)**		
	On postoperative Day 1, the operating surgeon will assess the postoperative hemostatic efficacy compared to that expected for the type of procedure performed in a non-hemophilic population	
Rating	**Criteria**	
Excellent	Postoperative blood loss was less than or equal to (≤100%) that expected	
Good	Postoperative blood loss was up to 50% more (101-150%) than expected	
Fair	Postoperative blood loss was more than 50% (>150%) of that expected	
None	Significant postoperative bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy	

Table 7
Perioperative Efficacy Assessment Scale (at discharge or 14 days post-surgery, whichever is first)

	At discharge or 14 days post-surgery, whichever is first, a hematologist will assess the perioperative efficacy compared to that expected for the type of procedure performed in a non-hemophilic population	
Rating	**Criteria**	
Excellent	Perioperative blood loss was less than or equal to (≤100%) that expected Required blood components for transfusions were less than or similar to that expected	
Good	Perioperative blood loss was up to 50% more (101-150%) than expected Required blood components for transfusions were less than or similar to that expected	
Fair	Perioperative blood loss was more than 50% of that expected (>150%) Required blood components transfusions were greater than that expected	
None	Significant perioperative bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy Required blood components for transfusions were substantially greater than expected	

22.5.2 Intra- and Postoperative Blood Loss

The observed versus predicted operative blood loss will be described for the period from initiation of the intervention to discharge or 14 days after the intervention, whichever is first.

Prior to the surgery, the surgeon/investigator will predict the estimated volume (mL) of the expected average and maximum blood loss for the planned surgical intervention in a hemostatically normal individual of the same sex, age, and stature as the study subject, for intraoperative, postoperative and overall perioperative time periods. Every effort should be made to predict the volume as precisely as possible, also taking into account, for example, the use of a tourniquet or placement of a postoperative drain and whether or not suction is used. The estimate will be for the intraoperative time period, the postoperative time period from completion of the procedure until approximately 24 hours post-surgery and for the overall perioperative time period (assessed at discharge or 14 days after the intervention, whichever is first).

The intraoperative blood loss will be measured by determining the volume of blood and fluid removal through suction into the collection container (waste box and/or cell saver) and the estimated blood loss into swabs and towels during the procedure, per the anesthesiologist's record. Postoperatively, blood loss will be determined by the drainage volume collected, which will mainly consist of drainage fluid via vacuum or gravity drain, as applicable. In cases where no drain is present, blood loss will be determined by the surgeon's clinical judgment, as applicable or entered as "not available".

Table 8
Flow Diagram of Surgical Procedures For Baxalta Clinical Study 261303

1.Prior to surgery

The following procedures should be performed before surgery and must be available at the latest by 2 hours before the start of surgery:

- Accurate prediction of volume of expected blood loss intraoperatively, postoperatively (from completion of the procedure until approximately 24 hours post-surgery) and for the overall perioperative time period (start of surgical procedure up to discharge)
- Outline the expected FVIII substitution plan with target peak and trough levels.

1.1 Loading Dose and Post Infusion Laboratory Assessment

Subjects will undergo the following procedures:

Prior to initial BAX 855 loading dose:

- Record AEs, concomitant medication and non-drug therapy use
- Physical examination, vital signs (pulse, respiratory rate, blood pressure and temperature) and weight
- Laboratory Assessments including:
    - Hematology (without differential but including platelets)
    - Clinical Chemistry
    - Within 30 minutes before loading dose, optional blood draw for:
        - FVIII activity and aPTT

Give loading dose within the 60 minutes prior to surgery:

- Loading dose of BAX 855 to raise the plasma level of FVIII to 80–100% of normal for major and to 30-60% for minor surgical, dental and invasive procedures. Administer within 60 minutes prior to surgery (prior to incision/intubation).

15±5 minutes after infusion of loading dose:

- Laboratory assessment of FVIII activity and aPTT
- Vital signs (pulse, respiratory rate, blood pressure and temperature) will be recorded 15 ±5 minutes after infusion

  If aPTT not normalized or desired FVIII level not obtained, rebolus of BAX 855 as necessary.
  If FVIII activity results are not available within a reasonable time period prior to the start of surgery, at least the post-infusion value of aPPT must be obtained. The FVIII activity level must be obtained within 4 hours after infusion of BAX 855 and dose adjustments must be performed as needed.

  The surgery can begin only if aPTT has normalized.

Table 8
Flow Diagram of Surgical Procedures For Baxalta Clinical Study 261303

2. Intraoperative Procedures

During the surgical procedure:

- Record AEs and concomitant medication and non-drug therapy use
- Record blood product usage, including salvaged blood, packed red blood cells (pRBC), platelets, and other blood products.
- Administer additional BAX 855 infusions according to the FVIII substitution plan
- Record intraoperative blood loss and transfusion requirements

If the subject has excessive or unexplained bleeding, blood draws for:

- FVIII activity
- FVIII inhibitory and binding antibodies

Treat by whatever means necessary until adequate hemostasis is achieved. If other FVIII concentrates become necessary, the subject will subsequently be withdrawn from the study.

After the surgical procedure:

- Record the volume of blood loss during surgery and total blood product usage, including salvaged blood, packed red blood cells (pRBCs), platelets, and other blood products
- Assess intraoperative hemostatic efficacy at the end of surgery (Table 5)
- If the subject is undergoing **major** surgery take sample for FVIII activity within preferably 6-8 h following surgery and within 12 hours at the latest, with dose adjustments as necessary on the day of surgery.

3. Postoperative Procedures

- For subjects undergoing major surgery: keep pre-infusion FVIII levels at least at 80% of normal for the first postoperative 72 hours and at least at 50% during postoperative Day 4-Day 7. From Day 8 until discharge the FVIII levels should not fall below 30% or according to the substitution plan.
- Subjects undergoing minor surgery can be re-dosed postoperatively with BAX 855 at 8-24 hour intervals. Keep trough levels of FVIII at 30–60% for the first 24 hours (or longer as deemed necessary). Give at least 1 postoperative dose or according to the substitution plan.

From Postoperative Day 1 (i.e., the day following the day of the surgical/invasive procedure), and daily until discharge the following assessments will be performed:

- Record AEs and concomitant medication and non-drug therapy use
- Record blood loss on a daily basis and at drain removal, if applicable
- Record transfusion requirements
- Hemostatic Efficacy Assessment:
  - Table 6: assessment of postoperative hemostatic efficacy of BAX 855 performed at Day 1 by the operating surgeon/investigator
  - Table 7: assessment of perioperative hemostatic efficacy of BAX 855 at day of discharge or Day 14, whichever occurs first, performed by the investigator

  If a subject leaves the facility on the day of the surgery/invasive procedure, he/she is required to have a site visit the next day to perform the assessments of postoperative and perioperative hemostatic efficacy.

Table 8
Flow Diagram of Surgical Procedures For Baxalta Clinical Study 261303

- Perform physical examination and vital signs (pulse, respiratory rate, blood pressure and temperature) on Day 1, 2, 3 and 7 post surgery (if a subject remains admitted)
- Blood draws for FVIII activity determination and hematology should be performed coincident with an early morning dose to the greatest extent possible.
- FVIII activity assays at the local and the central laboratories (back-up sample) on each day of planned IP administration at least once per day pre infusion (within 30 minutes) and post infusion (15 ±5 minutes), and prior to any unscheduled BAX 855 infusion
  - 1-stage clotting and chromogenic for the central laboratory
  - 1-stage clotting or chromogenic (whichever is available) for local laboratories
- Samples for central laboratory testing will be taken daily during Day 1 to 7 post-surgery and later then once weekly:
  - Hematology
  - FVIII activity
  - Clinical chemistry to be taken at Day 1 and then weekly
- If the subject has excessive or unexplained bleeding, blood draws for:
  - FVIII activity
  - FVIII inhibitory and binding antibodies

Table 9
Schedule of Study Procedures and Assessments for Surgery

	Preoperative	Intraoperative	Postoperative: Daily
Procedure/ Assessment	**~2 h Prior to Surgery**	**In OR**	
Medications and non-drug therapies	x	x	x
Physical examination	x		x Days 1, 2, 3 and 7, then weekly
Adverse events	x	x	x
Vital signs	x[e]	x[a] (as required)	x[a] Days 1, 2, 3 and 7
FVIII substitution plan	x		
IP treatment	x loading dose	x (as required)	x (as required) Give at least 1 postop dose
Hemostatic efficacy assessments		Table 5	Table 6 at Day 1 Table 7 at 14 days or on discharge x [b]
Blood loss	X predicted	x	x
Transfusion requirements		x	x
Laboratory Assessments			
FVIII activity (clotting *and* chromogenic assay at central lab; *either* clotting *or* chromogenic assay at local lab)	L and C within 30 min before loading dose, then 15 ±5 min after loading dose	Optional sampling, as deemed necessary: L C Also, if subject has excessive or unexplained bleeding	L and C[c]
aPTT	L and C[d] Same timepoints as for FVIII activity		
Immunogenicity		C (L)[e]	C (L)[e]

Key: C = central laboratory; L = local laboratory;

[a] Within 30 min pre, 15 ±5 min post-dose

[b] Whichever is first.

[c] If underwent major surgery take sample within preferably 6-8 h following surgery and within 12 h at the latest. Sample on each day of planned IP administration at least once per day pre infusion (within 30 minutes) and post infusion (15 ±5 minutes), and prior to any unscheduled BAX 855 infusion. Also if subject has excessive or unexplained bleeding.

[d] Surgery may only start if aPTT has normalized.

[e] Only if subject has excessive or unexplained bleeding: FVIII inhibitory and binding Ab.

23. DEFINITIONS

23.1 Joint Bleeds

Features of an acute joint bleed include some or all of the following: 'aura', pain, swelling, warmth of the skin over the joint, decreased range of motion and difficulty in using the limb compared with baseline or loss of function.

The earliest clinical signs of a joint bleed are increased warmth over the area and discomfort with movement, particularly at the ends of range.

Later symptoms and signs include pain at rest, swelling, tenderness, and extreme loss of motion.

In patients with advanced arthropathy it may be difficult to distinguish pain-related arthritis from that associated with an acute bleed. Rapid resolution of pain following infusion of factor concentrates (typical of an acute hemarthrosis) or improvement of pain associated with activity soon after a period of rest (typical of chronic arthritis) can help distinguish between the 2.

In infants and young children, reluctance to use the limb alone may be indicative of a joint/muscle bleed.

23.2 Muscle Bleeds

Muscle bleeds can occur in any muscle of the body, usually from a direct blow or a sudden stretch. A muscle bleed is defined as an episode of bleeding into a muscle, determined clinically and/or by imaging studies, generally associated with pain and/or swelling and functional impairment over baseline.

For further definitions of CNS, GI and abdominal hemorrhages see the Guidelines for the management of hemophilia from the world federation of hemophilia.[30,32]

23.3 Radiologic Classification of Changes

Using the score system below, the severity of arthropathy may be assessed in a single joint, in a single subject, or in a group of subjects [31]:

Table 10
Radiologic Classification of Changes

Radiologic Change	Finding	Score (Points)
Osteoporosis	Absent Present	0 1
Enlargement of epiphysis	Absent Present	0 1
Irregularity of subchondral surface	Absent Slight Pronounced	0 1 2
Narrowing of joint space	Absent <50% >50%	0 1 2
Subchondral cyst formation	Absent 1 cyst >1 cyst	0 1 2
Erosions at joint margins	Absent Present	0 1
Incongruence between joint surfaces	Absent Slight Pronounced	0 1 2
Deformity (angulation and/or displacement of articulating bones)	Absent Slight Pronounced	0 1 2

Possible joint score: 0-13 points.

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25. SUMMARY OF CHANGES

Protocol 261303: Amendment 5 2016 OCT 18
Replaces: Amendment 3 2015 SEP 04

In this section, changes from the previous version of **Amendment 3**, dated **2015 SEP 04**, are described and their rationale is given.

1. **Throughout the document**
   Description of Change: Minor grammatical and/or administrative changes have been made, including additional safety details sections added/revised according to the current Baxalta protocol template (i.e., Sections 2, 13.2.1.2, and 13.2.7).
   Purpose for Change: To improve the readability and/or clarity of the protocol, and to address updates from the current Baxalta protocol template.

2. **Section 1 Study Personnel and Investigator Acknowledgement Page**
   Description of Change: The sponsor's authorized representative was changed.
   Purpose for Change: To reflect current responsibilities.

3. **Synopsis, Active Product;**
   Section 8.2, Overall Study Design;
   Section 8.7.5, BAX 855 Prophylaxis Dosing;
   Figure 1, Study Design for Baxalta Clinical Study 261303;
   Section 21.2, Detailed Flow Diagram of Study Procedures;
   Section 13.1, Immunogenicity; Figure 2, Study Flow Chart;
   Section 21.2, Detailed Flow Diagram of Study Procedures;
   Section 21.3, Schedule of Study Procedures and Assessments;
   Section 21.4, Clinical Laboratory Assessments
   Description of Change: The washout periods have been revised to be consistent with the infusion interval according to the treatment regimen provided to the subject
   Purpose for Change: To account for the fact that some subjects have dosing frequencies based on their individual PK which differ from the twice weekly (low trough arm) or every other day (high trough arm) schedule.

4. **Synopsis, Subject Selection;**
   Section 9.1.2, Inclusion Criteria for Newly Recruited Subjects
   Description of Change: It is clarified that in case of a historically documented FVIII clotting activity performed by a certified clinical laboratory, FVIII gene mutation can only optionally support the finding of a severe hemophilia A.
   Purpose for Change: To ensure that no subject is enrolled on FVIII gene mutation result only.

5. **Section 6.3, Population to be Studied;**
   Section 6.4.2, Findings from Clinical Studies;
   Section 6.5, Evaluation of Anticipated Risks and Benefits of the Investigational Product to Human Subjects
   Description of Change: Reference to Phase 3 pediatric, continuation, and surgery studies added, including overall summary of safety from IB.
   Purpose for Change: Updated based on new available data.

6. **Section 7.3.3, Pharmacokinetics;**
   Section 8.1, Brief Summary;
   Section 8.7.4, BAX 855 Dosing for PK Assessment;
   Section 12.1, Pharmacokinetics;
   Figure 2, Study Flow Chart;
   Section 21.2, Detailed Flow Diagram of Study Procedures;
   Section 21.3, Schedule of Study Procedures and Assessments;
   Section 21.4, Clinical Laboratory Assessments
   Description of Change: The repeat PK after 9 months ±2 weeks of PK-guided prophylactic treatment is no longer mandatory, but optional.
   Purpose for Change: To reduce the burden on patients due to repeated study visits including blood draws over 96 h required for a repeat PK constituting a barrier for recruitment.

7. **Section 8.2, Overall Study Design;**
   Section 10.5, Subject Diary and Patient Reported Outcomes
   Description of Change: Data on type and duration of physical activity with a risk category of 2.5 or higher or contact sport will also be collected.
   Purpose for Change: To evaluate potential differences in type and extent of physical activity in the 2 treatment arms.

8. **Section 8.3, Duration of Study Period(s) and Subject Participation**
   Description of Change: Length of recruitment period has been revised.
   Purpose for Change: To reflect the current date of planned completion of recruitment.

9. **Section 8.7.2, Administration;**
   Section 12.2 Incremental Recovery (IR);
   Section 21.2, Detailed Flow Diagram of Study Procedures;
   Section 21.3, Schedule of Study Procedures and Assessments
   Description of Change: 1) In a subset of subjects the evaluation of at least one IR will be performed using 3000 IU potency vials instead of 500 or 1000 IU potency vials. 2) The dose to determine IR has been revised. Instead of a set dose of 60 ±5 IU, the PK-guided prophylactic dose of BAX 855 will be used.
   Purpose for Change: 1) To also evaluate the IR of a higher potency. 2) To ensure that subjects continue to receive the same PK-guided prophylactic dose and to measure the FVIII peak levels of the assigned dose.

10. **Section 8.7.5, BAX 855 Prophylaxis Dosing;**
    Section 8.7.6, BAX 855 Dose and/or Frequency Adjustments
    Description of Change: 1) Updated to detail revised dose adjustment approach, including revised calculations. 2) The weight for dose calculation and recalculation will be determined at each study visit.
    Purpose for Change: 1) To also handle the case that the trough levels used for dose adjustment were due to different doses. The former formula would only handle the case of the same dose being used for all infusions as required per protocol. 2) To ensure that the dose is continuously aligned with the subject's weight changes, if applicable.

11. **Section 8.7.7, Treatment of Bleeding Episodes**
    Description of Change: The anticipated recovery to be used in the absence of an individual recovery has been revised.
    Purpose for Change: To be consistent with already approved prescribing information.

12. **Section 10.5.1, Patient Reported Outcomes**
    Description of Change: Description of EQ-5D questionnaire amended to reflect 3 levels for each of the 5 measured dimensions.
    Purpose for Change: Correction of error in original text.

13. **Section 11.1.3, Hemophilia Joint Health Score (HJHS);**
Section 11.1.4 X-ray of Impaired Joints;
Section 21.2, Detailed Flow Diagram of Study Procedures, Visits at Study Site;
Section 21.3, Schedule of Study Procedures and Assessments;
Section 23.3, Radiologic Classification of Changes
Description of Change: 1) The X-ray of an impaired joint was removed from Section 11.1.3 HJHS and a new Section regarding the conductance of an X-ray was added. 2) Definition for impaired joint requiring conductance of an X-ray was provided based on the HJHS scoring system. 3) Already existing X-rays of impaired joints not older than 12 months can be used. The repeat X-ray of the impaired joint after 12 months was removed. 4) The Pettersson Score was added to describe the radiologic findings.
Purpose for Change: 1) To account for the fact that X-ray is not part of the HJHS. 2) To provide a definition for a clinically impaired joint. 3) No radiologic changes are expected after 12 months of prophylactic treatment. 4) To have a consistent description of radiologic findings of the impaired joint.

14. **Section 13.1, Immunogenicity;**
Section 13.2.1.1, Serious Adverse Event
Description of Change: 1) In order to meet the definition of an SAE, the FVIII inhibitor has to be confirmed at the central laboratory. 2) Details were provided when to evaluate FVIII IgG subclass 1-4 and IgA, and IgE antibodies to FVIII and PEG-FVIII.
Purpose for Change: 1) To account for different threshold levels at the various local laboratories. 2) To provide instructions when to assess FVIII IgG subclass 1-4 and IgA as well as IgE antibodies.

15. **Section 13.9.1.1, Blood Type**
Description of Change: The measurement of blood type will be performed at the local laboratory.
Purpose for Change: The central laboratory does not offer blood type testing.

16. **Section 13.9.1.5, Viral Serology**
Description of Change: Viral serology can also be performed whenever clinically indicated.
Purpose for Change: To ensure that viral serology will be measured centrally whenever clinically indicated.

17. **Section 13.9.6, Biobanking;**
    Section 21.4, Clinical Laboratory Assessments
    Description of Change: Further exploratory testing will be related to biomarkers for hemophilia.
    Purpose for Change: To provide clarity about the purpose of the additional blood draws for exploratory testing.

18. **Section 16.1, Investigator's Responsibility**
    Description of Change: Detail added regarding the trial being conducted in accordance with the Helsinki declaration.
    Purpose for Change: To meet a regulatory request.

19. **Section 21.3, Schedule of Study Procedures and Assessments;**
    Section 21.4, Clinical Laboratory Assessments
    Description of Change: Table amended to clarify that the washout period at Baseline is 72-96 h.
    Purpose for Change: Error in Protocol Amendment 3.

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: BAX 855 – Pegylated Full-Length Recombinant Factor VIII

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

PROTOCOL IDENTIFIER: 261303

CLINICAL TRIAL PHASE 3

AMENDMENT 5: 2016 OCT 18

Replaces: AMENDMENT 3: 2015 SEP 04

ALL VERSIONS:
AMENDMENT 5: 2016 OCT 18
AMENDMENT 4: 2015 OCT 30 (Austria)
AMENDMENT 3: 2015 SEP 04
AMENDMENT 2: 2015 MAY 12
AMENDMENT 1: 2015 MAR 20
ORIGINAL: 2015 JAN 13

OTHER ID(s)
NCT Number: To be Determined
EudraCT Number: 2014-005477-37
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 Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
PPD , MD
PPD
Global Clinical Development Operations