Clinical Study Protocol

NCT Number : NCT02615691

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

Study Number: 261203

Document Version and Date: Amendment 8, 21 June 2021

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

CLINICAL STUDY PROTOCOL

PRODUCT: TAK-660 (BAX 855) – PEGylated full-length recombinant factor VIII

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

STUDY SHORT TITLE: BAX 855 PUP
PROTOCOL IDENTIFIER: 261203
CLINICAL TRIAL PHASE 3

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Study Sponsor(s):

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* Baxalta is a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], Ph.D.
[redacted] Clinical Sciences
Takeda Pharmaceutical Company Limited

1.2 Study Organization

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

2. SERIOUS ADVERSE EVENT REPORTING

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

**ALL SAEs 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.**

See SAE Protocol Sections for further information and SAER form for contact information.
Further details are also available in the study team roster.

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

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

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	TAK-660 (BAX 855)
Name(s) of Active Ingredient(s)	PEGylated full-length recombinant factor VIII
CLINICAL CONDITION(S)/INDICATION(S) • Treatment and prevention of bleeding in severe hemophilia A	
PROTOCOL ID	261203
PROTOCOL TITLE	Phase 3, prospective, multi-center, open label study to investigate safety, immunogenicity and hemostatic efficacy of PEGylated factor VIII (BAX 855) in previously untreated patients (PUPs) < 6 years with severe hemophilia A (FVIII < 1%)
Short Title	BAX 855 PUP
STUDY PHASE	Ph3
PLANNED STUDY PERIOD	
Initiation	First subject in: Q4 2015
Primary Completion	**Interim analysis** (50 subjects with 50 exposure days [EDs] to BAX 855) of Part A (main study): Q1 2019 **Final analysis** Part A (main study): Q4 2020 Part B [immune tolerance induction (ITI)]: Q2 2023
Study Completion	**Interim analysis** Part A (main study): Q2 2019 **Final analysis** Part A (main study): Q1 2022 Part B (ITI Q4 2023)
Duration	Part A: 5 years (enrollment approximately 3 years, treatment approximately 2 years, depending on the type of treatment)* Part B: Approximately 3.5 years (until immune tolerance success, failure or a maximum of 33 months, whichever occurs first. In case of success, 5-6 additional months for transitioning to twice weekly prophylaxis including a three-month follow-up period)* * For optional extended access to BAX 855, refer to Section 8.3.
STUDY OBJECTIVES AND PURPOSE	
Study Purpose • To investigate safety, immunogenicity and hemostatic efficacy of PEGylated recombinant FVIII (BAX 855) in previously untreated patients (PUPs) <6 years of age with severe hemophilia A (baseline FVIII level <1%) and <3 EDs to ADVATE, BAX 855 or plasma transfusion.	

Primary Objective

- The primary objective is to determine safety including immunogenicity of BAX 855 based on the incidence of inhibitor development to FVIII (≥0.6 Bethesda units (BU)/mL using the Nijmegen modification of the Bethesda assay)

Secondary Objectives

Safety

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

Hemostatic Efficacy

- To assess the efficacy of prophylactic treatment with BAX 855
- To characterize the efficacy of BAX 855 in the control of bleeding episodes
- To evaluate the efficacy of BAX 855 for perioperative management, if surgery is required

Pharmacokinetics

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

Objectives for ITI:

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

Exploratory Objectives

- [redacted]
- [redacted]

Additional Exploratory Objective for ITI

- [redacted]

STUDY DESIGN

Study Type/ Classification/ Discipline	Safety, Immunogenicity, Hemostatic Efficacy, and Pharmacokinetic
Control Type	Uncontrolled
Study Indication Type	Prevention, Treatment
Intervention model	Single arm with 2 sub-arms (surgery, ITI)
Blinding/Masking	Open-label

Study Design	This study is a Phase 3, prospective, open-label, multicenter study to assess the safety, immunogenicity and hemostatic efficacy of BAX 855 in previously untreated patients (PUPs) <6 years of age with severe hemophilia A (baseline FVIII level <1%) and <3 EDs to ADVATE, BAX 855 or plasma transfusion in at least 100 evaluable subjects
Planned Duration of Subject Participation	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 ITI therapy is required* * For optional extended access to BAX 855, refer to Section 8.3.

Primary Outcome Measure

- Incidence of FVIII inhibitor development

Secondary Outcome Measure(s)

Safety:

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

Efficacy:

- Annualized bleeding rate (ABR) for prophylactic and on-demand treatment
- Number of BAX 855 infusions per bleeding episode
- Overall hemostatic efficacy rating at 24 h after initiation of treatment and at resolution of bleed
- Weight-adjusted consumption of BAX 855 per month, per year and per event (prophylaxis, treatment of bleeding episode, surgery) and the number of infusions per month and per year
- Assessment of intra-, post- and perioperative hemostatic efficacy in case of surgery
- Intra- and postoperative blood loss in case of surgery

Pharmacokinetics:

- IR at baseline and over time
- Half-life at baseline (optional)[i]

Additional Outcome Measures for ITI:

- **Primary**: The success rate of ITI therapy with BAX 855[ii]

[i] Based on abbreviated PK using 2 post-infusion timepoints: 15-30 minutes and 24–48 hours

[ii] Success is defined as 1) a persistently negative inhibitor titer <0.6 BU, 2) FVIII IR ≥66% of baseline value, following a wash-out period of 84 – 96 h, and 3) a FVIII half-life of ≥6 hours. If no baseline IR is available, the IR value is indicative of an adequate clinical response following a wash-out period of 84-96 hours. An adequate clinical response is defined as pharmacokinetic parameters that permit effective prophylactic treatment of the study subject, including maintenance of FVIII levels above 1%.

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

Exploratory Outcome Measures

[redacted]

INVESTIGATIONAL PRODUCT, DOSE AND MODE OF ADMINISTRATION

Active Product	**BAX 855** **Dosage form**: injection, powder, lyophilized, for solution **Dose and Dosage frequency**: **Part A (main study):** On-demand: 10-50 IU/kg, up to 80 IU/kg, depending on the severity of the bleeding episode. Subjects may start with on-demand therapy if they are younger than 3 years and if they have not experienced 2 joint bleeds. Prophylaxis: To be initiated before the age of 3 years or after a maximum of 2 joint bleeds, whichever occurs first, at a dose of 25-50 IU/kg, up to 80 IU/kg at investigator discretion, at least once weekly. **Surgery (Part A):** The dose and frequency of BAX 855 administered will be individualized based on the subject's BAX 855 IR and half-life, if available, to obtain the target level required for the type of the surgery, dental or other invasive procedure being performed. In general, for major surgery initial FVIII target levels in plasma should be ≥80-100% of normal FVIII level, whereas for minor surgery target FVIII levels should be ≥30-60%.

[iii] Partial success is defined after 33 months of ITI. Two of the following criteria must be met: 1) inhibitor titer <0.6 BU (confirmed by a central laboratory with a second blood specimen obtained within 2 months), 2) FVIII IR ≥66% of baseline value (confirmed within a 2-month period), and 3) FVIII half-life ≥6 hours. If no baseline IR is available, the IR value determined after a wash-out period of 84-96 h is indicative of an adequate clinical response. An adequate clinical response is defined as pharmacokinetic parameters that permit effective prophylactic treatment of the study subject, including maintenance of FVIII levels above 1%.

[iv] Failure is defined as the failure to meet the criteria for success or partial success within 33 months of ITI therapy OR less than 20% reduction in inhibitor titer, relative to the peak inhibitor titer (in the absence of infection which in the opinion of the investigator could be expected to result in elevated inhibitor titers), over any 6-month period after the first 3 months of treatment.

	Part B (ITI): daily 100-200 IU/kg or 3 x weekly 50 IU/kg. In case of success, high-dose ITI regimen, if applicable, will be reduced to twice weekly prophylaxis as follows: • 100 ± 5 IU/kg/day for the first 4 weeks; then • 50 ± 5 IU/kg/day for a further 4 weeks; then • 50 ± 5 IU/kg every second day for a further 4 weeks; then • 50 ± 5 IU/kg administered twice a week, adjusted as needed to maintain a FVIII trough level of 1%, for a further 3 months. Subjects receiving low dose ITI therapy with 3 x 50 IU/kg weekly will be transitioned to twice weekly 50 IU/kg, adjusted as needed to maintain a FVIII trough level of 1%, for a further 3 months. After this period, a Completion/Termination Visit will be performed. **Mode of Administration**: intravenous bolus
SUBJECT SELECTION	
Targeted Accrual	At least 100 evaluable subjects; approximately 120 subjects will be dosed to allow for dropouts
Number of Groups/Arms/Cohorts	1

Inclusion Criteria

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

Additional inclusion criteria for Part B (ITI):

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

Exclusion Criteria

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

[v] BAX 855 refers to commercial BAX 855 in those countries where licensed at the time the study is performed.

[vi] If a subject is close to weighing 5 kg at screening and will have reached a weight of at least 5 kg at the baseline visit, the subject is eligible for participation.

[vii] The use of systemic immunomodulating drugs (eg, anti-CD20 chimeric monoclonal antibody rituximab) as part of ITI therapy with BAX 855 is permitted.

Additional exclusion criteria for Part B (ITI)

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

STATISTICAL ANALYSIS

Sample Size Calculation

The sample size of 100 subjects followed for 100 EDs originates from EMA/CHMP/BPWP/144533/2009; it is not based on statistical considerations.

Planned Statistical Analysis

For the analysis of the primary outcome measure, incidence of FVIII inhibitor development, a Clopper-Pearson exact 95% confidence interval (CI) will be computed for the proportion of subjects who developed FVIII inhibitors. The set of subjects to be analyzed includes all subjects who developed an inhibitor (at any time) confirmed by a central laboratory based on a second repeat blood sample drawn within 2 weeks of site notification of an inhibitor and all subjects who did not develop an inhibitor and had ≥100 EDs. An interim analysis is planned after 50 subjects have completed 50 EDs or have developed a confirmed FVIII inhibitor.

Binding antibodies to FVIII, BAX 855 and PEG and all other secondary safety outcome measures will be analyzed descriptively.

The ABR will be analyzed by point and interval estimates derived from a negative binomial model with treatment regimen (on-demand vs. prophylaxis) as a covariate and the duration of the observation period as an offset. Other secondary efficacy outcome measures as well as IR over time will be analyzed descriptively.

Outcomes of ITI will be summarized descriptively. Separate analyses of data from subjects dosed with the 2 dosing regimens of 50 IU/kg 3 x weekly and 100-200 IU/kg daily will be performed. The analysis of efficacy will be stratified by subjects who received BAX 855 as a single agent for ITI and subjects who used BAX 855 plus an immune modulatory agent, if applicable.

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5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	Annualized bleeding rate
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase (SGOT)
BAX 855	Former product code name for PEGylated recombinant FVIII (rFVIII), now TAK-660
B19V	Parvovirus B19
BU	Bethesda unit
BUN	Blood urea nitrogen
(US) CFR	(US) Code of Federal Regulations
CHO	Chinese hamster ovary
CI	Confidence interval
(e)CRF	(electronic) case report form
CVD	Central venous device
DMC	Data Monitoring Committee
EC	Ethics committee
ED	Exposure day
EDTA	Ethylene diamine tetra acetic acid
EEA	European Economic Area
FVIII	Factor VIII
GCP	Good Clinical Practice
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G

Abbreviation	Definition
IgM	Immunoglobulin M
IP	Investigational product
IR	Incremental recovery over time
ITI	Immune tolerance induction
IU	International unit (s)
i.v.	Intravenous(ly)
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MRT	Mean residence time
MTP	Minimally treated patient
NMC	Non-medical complaint
PEG	Polyethylene glycol
PK	Pharmacokinetic(s)
PRBC	Packed red blood cells
PTP	Previously treated patient
PUP	Previously untreated patient
rFVIII	Recombinant factor VIII
rSDV	Remote source document verification
SAE	Serious adverse event
SAER	Serious adverse event report
SIC	Subject identification code
SI	Serious injuries
SWFI	Sterile water for injection
TAK-660	Product code name for PEGylated recombinant FVIII (rFVIII), formerly BAX 855
UADE	Unexpected adverse device events
US	United States

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

The investigational product (IP), TAK-660 (hereafter referred to as BAX 855), is a polyethylene glycol (PEG)-ylated full-length recombinant factor VIII (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.

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 pharmacokinetic (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.

BAX 855 consists of rFVIII protein molecules (octocog alfa, ADVATE) with covalently bound PEG chains with a molecular weight of 20 kDA 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 from which it is derived. Comprehensive preclinical studies as well as a completed Phase 1 study (Study 261101) and pivotal Phase 2/3 study (Study 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 one-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).

The current study is a Phase 3, prospective, uncontrolled, multicenter study to evaluate the inhibitor risk in previously untreated patients (PUPs) receiving BAX 855 and summarize any association with genetic or other risk factors. It will also evaluate the outcome of immune tolerance induction (ITI) therapy with BAX 855 in those subjects who have developed a FVIII inhibitory antibody necessitating ITI. At least 100 pediatric subjects <6 years with severe hemophilia A will be followed up for a minimum of 100 exposure days (EDs) or until they have developed confirmed inhibitory antibodies to FVIII.

No comparator drug product will be used in this study for prophylaxis or treatment of bleeding. The efficacy of on-demand dosing for treatment of bleeding episodes in the range of 10-60 IU/kg has been generated in the completed Phase 2/3 pivotal BAX 855 study (range 6.8 to 61.4 IU/kg). Doses as high as 80 IU/kg may be used for the treatment of bleeding episodes based upon experience with these doses with ADVATE.

The vast range of prophylactic dosing between 25-80 IU/kg with varying frequencies but at least once weekly reflects the range of treatment approaches in this very young patient population across hemophilia centers and countries. Early initiation of once weekly infusions of 25 IU/kg before the establishment of a severe bleeding pattern and thus avoiding intensive treatment may minimize immune stimulation which may reduce the risk for inhibitor development. After 50 EDs the dose and/or frequency may be increased.[4] Also starting very early in life with once weekly prophylactic infusions may avoid the need for surgical implants which may become necessary in case of increased frequency of infusions. Once the patient is older, frequency can be increased, often without the need for a central venous device (CVD).[5] The Canadian regimen, which is a tailored-dose/dose-escalation prophylactic regimen, starts with once weekly infusions of 50 IU/kg which is adjusted according to the patient's bleeding pattern. Dose and frequency are changed to twice weekly infusions of 30 IU/kg once the subject develops a target joint. This may be further increased to 25 IU/kg q2 days using regular FVIII concentrates.[6]

In the completed BAX 855 Phase 2/3 pivotal study a dose of 45 ± 5 IU/kg twice weekly demonstrated that it is efficacious to reduce or prevent bleeding episodes; in the Phase 3 pediatric PTP study the dose consisted of twice weekly infusion of 50 ± 10 IU/kg which could be increased to 80 IU/kg. The Phase 3 continuation study employed the same dosing regimens as in the pivotal and pediatric studies, but also allowed a q5 and q7 dosing based on the bleeding pattern of the patients in doses up to 80 IU/kg.

The recommended dosing regimens for ITI therapy of 3 x 50 IU/kg weekly to 100-200 IU/kg daily are based on the results of the International ITI study which randomized patients with high titer inhibitors to a high dose regimen consisting of daily infusions of 200 IU/kg or a low dose regimen of 3 x 50 IU/kg weekly using a plasma-derived or recombinant FVIII concentrate.[7] The success rate did not differ between treatment arms but the times taken to achieve negative titers were shorter using the high dose regimen. A dose of 100 IU/kg daily is also used in many hemophilia centers but has not been studied in randomized controlled trials.[8]

6.2 Clinical Condition/Indication

Hemophilia A is a congenital bleeding disorder caused by deficiency of FVIII and is treated by replacement therapy with FVIII concentrate. Current management of severe hemophilia A includes on-demand treatment for bleeding episodes and prophylaxis to prevent bleeds.[9] The

major objective of a prophylactic treatment in severe hemophilia A patients is to prevent bleeding episodes, in particular joint bleeding.

The intended indication for BAX 855 is treatment and prophylaxis of bleeding 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.[10]

Several studies have shown that prophylactic administration of FVIII from an early age prevents arthropathy but also other potentially life-threatening bleeds. Findings of a joint bleed in canine knees support the theory that a single hemarthrosis may result in permanent joint damage since every intra-articular bleed precipitates a biological cascade despite a rapid clearance of blood.[11] Astermark et al examined how the age that treatment is started affects joint outcome in patients with severe hemophilia (108 with hemophilia A and 13 with hemophilia B) and found that starting prophylaxis before the age of 3 years resulted in better outcomes as compared to age groups starting prophylaxis at either 3-5 years or 6-9 years, but emphasized that treatment can be individualized according to the clinical picture.[12] In a randomized study which enrolled 65 subjects between 1996 and 2000, it was found that prophylaxis (every other day) with rFVIII can prevent joint damage, as assessed by x-ray or MRI of bone or cartilage damage, with a decrease in the frequency of joint bleeds and other bleeds in young boys (<30 months of age) with severe hemophilia A.[13] Most of the children had fewer than 50 EDs at the time of enrollment. Of the 27 boys on prophylaxis, 25 (93%) had no joint damage compared to 16 of 29 (55%) with on-demand therapy. Two children in the prophylaxis group developed high titer FVIII inhibitor. Three subjects receiving on-demand therapy had life-threatening bleeds. A tailored prophylactic regimen based on initial once-weekly prophylaxis was found to be effective in a prospective study in 25 boys in Canada, with an average of 1.2 joint bleeds per person year and a rate of target joint bleeding of 0.09 per person-year. One subject developed a transient inhibitor.[6]

MASAC (Medical and Scientific Advisory Council from the National Hemophilia Foundation) recommends that prophylaxis be considered optimal therapy for patients with severe hemophilia A began at a young age consistent with primary prophylaxis.[9] Primary prophylaxis is the long-term continual treatment either started before the age 2 years or started prior to the onset of joint damage (presumptively defined as not more than one joint hemorrhage, irrespective of age). Secondary prophylaxis is defined as a long-term continual prophylaxis initiated after multiple joint bleeds and the onset of joint damage.[14]

6.2.1 Inhibitor Development and Immune Tolerance Induction (ITI)

The development of inhibitors to FVIII leads to serious complications of hemophilia therapy. The overall incidence of inhibitor development in PUPs is approximately 30% in patients with severe hemophilia A.[15] FVIII inhibitors are quantified according to the inhibition of FVIII

activity on the one-stage clotting assay, or the Bethesda assay with Nijmegen modification. High responder inhibitors with Bethesda titer >5 show an anamnestic response to re-exposure to FVIII, with an increase in antibody titer beginning 2-3 days post-exposure and peaking at 7-21 days.[16] Without immune tolerance therapy or immune suppression, high-titer inhibitors often persist even in the absence of continued FVIII exposure.

Patients with inhibitors have substantially increased morbidity and increased cost of care.[17,18] Individual and environmental risk factors for inhibitor formation have been identified including the causative FVIII gene mutation, family history, ethnicity, intensity of treatment, and the early implementation of prophylactic treatment.[19,20] Furthermore, mechanisms of inhibitor formation and conversely, tolerance to FVIII among patients with hemophilia who do not develop inhibitors, are not well understood, limiting the ability to develop rational therapies to overcome inhibitors. It is thought that signals released from damaged or inflamed tissue, as occurs during severe bleeds or surgery, result in enhanced antibody formation following activation of antigen-presenting cells.

FVIII inhibitors develop after the first few exposures to FVIII in PUPs. The median time to development of an inhibitor is within the first 9-10 days of exposure to FVIII.[21,22] Of those patients who eventually develop inhibitors, 50% develop them within the first 20 EDs, 95% within the first 50 EDs and >99% within the first 150 EDs.[23] A retrospective cohort study of 366 PUPs with severe hemophilia A in the multicenter European/Canadian Concerted Action on Neutralizing Antibodies in Severe Hemophilia A (CANAL) study did not identify FVIII product class or switch as a risk for inhibitor development.[24] The CANAL study also identified age at first exposure to FVIII to be a risk factor; however, this association disappeared in a multivariate analysis where intensity of treatment was considered. Early surgical procedures (relative risk (RR) 3.7, 95% confidence interval (CI) 2.0-7.1) and major “peak treatment episodes” with high doses of FVIII (RR 3.3, CI 2.1-5.3) were independently related to a higher risk of inhibitor development. Clinically relevant inhibitors developed in 24% of patients with 19% developing high-titer inhibitors. Further analysis suggested that initiation of scheduled FVIII infusions (prophylaxis) begun at a young age results in a 60% lower risk of inhibitor formation (RR, 0.4; CI, 0.2-0.8).[24] A study in 574 PUPs with severe hemophilia A investigated whether there is a difference in inhibitor development between recombinant and plasma-derived FVIII products over 75 EDs and also whether switching between products had an effect.[25] Inhibitory antibodies developed in 177/574 children (cumulative incidence, 32.4%); the cumulative incidence of high-titer inhibitors was 22.4%. There was a similar risk of inhibitor development with plasma-derived products and recombinant products (adjusted hazard ratio as compared with recombinant products, 0.96; 95% CI, 0.62 to 1.49). The only difference between products was found between second- and third-generation full-length recombinant products, with an increased risk of inhibitor development associated with second-generation products (adjusted hazard ratio,

1.60; 95% CI, 1.08 to 2.37). Switching between products did not increase the risk of developing inhibitors. Prophylaxis is the recommended approach in Germany and a review of the experiences at hemophilia centers in Frankfurt, Bremen and Munich in developing regimens that minimize the risk of inhibitor formation has shown that avoidance of immunological danger signals in the early stages of treatment may contribute to the low incidence of inhibitors in PUPs at these centers.[26] Such a regimen was tested in a pilot study in 26 PUPs and compared with historical controls.[4] The regimen consists of 25 IU/kg FVIII infused once weekly generally started early, preferably at ED 1. Fourteen of 30 subjects given standard prophylaxis but only 1 of the 26 subjects given the new regimen, starting with once-weekly 25–35 IU/kg, developed an inhibitor (P = 0.0003, OR 0.048, 95% CI: 0.001–0.372). In a report on the longer-term follow up of these patients after >150 EDs, no further patients developed an inhibitor.[27] However, these results could not be confirmed in the EPIC study (Early Prophylaxis Immunologic Challenge). Of 19 treated subjects, 8 developed confirmed inhibitors, 5 of which were low titers ranging from 0.6 to 1.5 BU/mL. Both subjects with a confirmed low titer of 0.6 BU/mL tested negative for binding antibodies to FVIII (IgA, IgM, IgG, IgG 1-4).[28] The lack of the concomitant presence of binding antibodies to FVIII indicates the potential need to clarify the real nature of borderline inhibitory activity.

In a prospective trial of 55 PUPs and minimally treated patients (MTPs) with severe/moderately severe hemophilia A (baseline FVIII ≤2%) treated with ADVATE given either prophylactically or on demand, inhibitory antibodies to FVIII developed in 16/55 (29.1%; 95% CI: 17.1%-41.1%) subjects.[29] The odds ratio (OR [95% CI]) of developing inhibitors was significantly higher in subjects with a family history of inhibitor (4.95 [1.29–19.06]), non-Caucasian ethnicity (4.18 [1.18–14.82]), and intensive treatment at high dose (4.5 [1.05–19.25]) (mean dose of ≥50 IU/kg/day for at least 5 consecutive days) within ≤20 EDs. The hemostatic efficacy, both to treat bleeds and for surgical prophylaxis, was established.

6.3 Population To Be Studied

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

Justification for enrollment of pediatric subjects is based on the requirements outlined in the International Conference on Harmonization (ICH) M3 and E11 guidelines.[30,31] Pediatric subjects are expected to benefit from a full-length rFVIII molecule with an extended half-life. Moreover, results from nonclinical repeated toxicology studies, the core safety pharmacology package, and the clinical studies performed with BAX 855 have not raised any safety or tolerability concerns. Also, according to the EMA guidelines[10], this clinical study in PUPs will not start until data are available from 20 PTPs <12 years participating in the pediatric Study 261202 who have been followed up for 50 EDs to BAX 855 including a minimum of 10 subjects <6 years, and when PK

investigations in children <12 years are completed. The data will be reviewed by an independent Data Monitoring Committee (DMC) before the start of the trial. Furthermore, the parent protein molecule ADVATE has been used extensively in the entire pediatric population with no unforeseen adverse events (AEs; see ADVATE package insert).

6.4 Findings from Nonclinical and Clinical Studies

6.4.1 Findings from Nonclinical Studies

Octocog alfa is expressed in Chinese hamster ovary (CHO) cells by a plasma/albumin free cell culture method and is the active substance in licensed product ADVATE. Thus, the viral safety of BAX 855 is ensured by the ADVATE bulk drug substance manufacturing process as any potential risk of contamination with viruses or adventitious agents during the subsequent manufacturing steps of BAX 855 has been minimized. No substances of animal or human origin are added throughout the entire manufacturing process of BAX 855.

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

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

6.4.2 Findings from Clinical Studies

A first-in-human prospective, open label, crossover, dose-escalation study to evaluate safety and PK parameters of single doses of BAX 855 compared to single doses of ADVATE was conducted in 19 adult PTPs with severe hemophilia A (FVIII <1%) (Study 261101). The mean half-life was 1.4- and 1.5-fold higher for BAX 855 compared to ADVATE in Cohorts 1 (30 IU/kg) and 2 (60 IU/kg), respectively, demonstrating an extended half-life for BAX 855 compared to ADVATE. No subjects developed inhibitory antibodies to FVIII or binding antibodies to FVIII, PEG-FVIII or PEG after a single BAX 855 infusion. There were no notable differences in the type or rate of AEs experienced by subjects after single infusions of ADVATE versus BAX 855. Based on these data, BAX 855 was shown to be safe and well tolerated after single dose administration, which supported the use of the BAX 855 dosing regimens planned in the Phase 2/3 Study 261201.

A pivotal, phase 2/3, multicenter, non-randomized open label study in 138 adult and adolescent ≥12 years male PTPs with severe hemophilia A demonstrated that BAX 855 is safe and efficacious in treating bleeding episodes on demand and in prophylaxis administered twice

weekly (45 ± 5 IU/kg) (Study 261201). BAX 855 extended the mean half-life by approximately 1.4-fold and MRT by approximately 1.5-fold as compared to known data for ADVATE and confirmed the data obtained in the Phase 1 study. Twice weekly prophylactic infusions resulted in an annualized bleeding rate (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. No FVIII inhibitory antibodies or persistent binding antibodies against FVIII, PEG-FVIII, PEG, or CHO proteins were reported, and no safety signals were identified.

An interim analysis of the surgery study (261204) in PTPs aged 2-75 years of age was performed once 15 surgeries in 15 subjects were completed. It was based on 11 major (3 knee replacements, 2 arthroscopic synovectomies, 1 elbow cyst extirpation, 3 multiple tooth extractions including 1 radicular cyst removal, 1 port placement, and 1 gastric band insertion) and 4 minor surgeries (1 synoviorthesis, 1 radiosynovectomy, 1 tooth extraction, and 1 dermatological). Results indicate that BAX 855 was efficacious and safe in the perioperative use in surgery with blood loss comparable to that expected for the same type of procedure performed in a non-hemophilic patient. No FVIII inhibitors were detected and no new safety issues have been identified.

The pediatric study performed in 66 PTPs <12 years of age, half of whom are <6 years old, evaluated safety, immunogenicity and efficacy over 50 EDs or 6 months, whichever occurred last. In a subset of subjects (at least 12 PTPs per age cohort) pharmacokinetics of BAX 855 were investigated. The continuation study (261302) further assessed efficacy and safety including immunogenicity in subjects who initially participated in the BAX 855 pivotal, pediatric or surgery study until they accumulated at least 100 EDs to BAX 855 across the studies. Additionally, a PK-guided dosing study (261303) evaluated efficacy and safety of 2 prophylactic treatment regimens targeting 2 different FVIII trough levels.

For further information, refer to the BAX 855 IB.

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

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

dizziness, paresthesia, rash, flushing, face swelling, urticaria, and pruritus.[viii] No adverse drug reactions other than those reported for ADVATE have been identified in the completed and ongoing clinical studies with BAX 855.

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 patients with hemophilia A. BAX 855 may react with pre-existing anti-PEG antibodies, potentially resulting in a clinical hypersensitivity reaction or increased clearance of BAX 855 from circulation. BAX 855 and ADVATE showed a similar immunogenicity profile in preclinical in vitro and in vivo studies. Data from preclinical studies indicate that PEGylated human FVIII can only induce antibodies against PEG when FVIII is recognized as a foreign protein that can provide immunogenic epitopes for CD4+ T cells.

Moreover, results from a tissue cross reactivity study show that even high-affinity antibodies against PEG do not cross-react with any human tissue. In the pivotal Phase 2/3 studies it could be demonstrated that the presence of anti-PEG or anti-BAX 855 antibodies at screening or transiently occurring in some subjects did not have an impact on hemostatic efficacy or safety.

The sponsor believes that the risk benefit profile for BAX 855 is acceptable based on the preclinical safety profile of BAX 855, the data from the Phase 1, Phase 2/3 pivotal, and interim data from the Phase 3 surgery study, as well as the hemostatic efficacy and safety data from the Phase 3 pediatric study in PTPs <12 years of age. Based on the comparability of BAX 855 to ADVATE, it is anticipated that the risk for inhibitor development in PUPs will be similar to that of ADVATE (29.1%; 95% CI: 17.1%-41.1%).[29]

Additional details related to risks and benefits can be found in the BAX 855 IB.

6.6 Compliance Statement

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

[viii] ADVATE Company Core Data Sheet on file at Takeda Development Center Americas, Inc. (Lexington, MA).

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

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

7.2 Primary Objective

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

7.3 Secondary Objectives

7.3.1 Safety

- To determine the immunogenicity of BAX 855 in terms of binding IgG and IgM antibodies to FVIII, PEG-FVIII and PEG
- To determine the safety of BAX 855 based on AEs and SAEs

7.3.2 Hemostatic Efficacy

- To assess the efficacy of prophylactic treatment with BAX 855
- To characterize the efficacy of BAX 855 in the control of bleeding episodes
- To evaluate the efficacy of BAX 855 for perioperative management, if surgery is required

7.3.3 Pharmacokinetics

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

7.3.4 ITI Objectives

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

7.4 Exploratory Objectives

- [redacted]
- [redacted]

Additional Exploratory Objective for ITI:

- [redacted]

8. STUDY DESIGN

8.1 Brief Summary

This study is a Phase 3, prospective, open-label, multicenter study to assess the safety, immunogenicity and hemostatic efficacy of BAX 855 in PUPs <6 years of age with severe hemophilia A (baseline FVIII level <1%) and <3 EDs to ADVATE, BAX 855[ix] or plasma in at least 100 evaluable subjects. Subjects will receive prophylactic and/or on-demand therapy with BAX 855 for at least 100 EDs or until they have developed a confirmed FVIII inhibitor (Part A). During Part A, subjects can undergo surgical or invasive procedures under a protocol-defined regimen for BAX 855. Subjects who develop a high titer FVIII inhibitor or subjects with low titer FVIII inhibitors where ITI therapy is necessary because of poorly controlled bleeding despite increased BAX 855 doses or bypassing agents are required to treat bleeding may enter Part B (ITI portion) of the study to undergo ITI therapy with BAX 855.

8.2 Overall Study Design

This study is a Phase 3, prospective, uncontrolled, open-label, multicenter study to assess the safety, immunogenicity and hemostatic efficacy of BAX 855 in a total of 100 evaluable PUPs <6 years of age with severe hemophilia A (baseline FVIII level <1%). The overall study design is illustrated in Figure 1. Approximately 120 subjects will be enrolled.

Subjects will be screened per protocol inclusion/exclusion criteria and, following confirmation of eligibility, will receive the first administration of BAX 855 at the study site during the baseline visit to determine IR (or the optional abbreviated PK assessment for half-life).

In the main study (Part A), subjects will complete study visits as follows to undergo safety, immunogenicity, and hemostatic efficacy assessments: Baseline Visit, Visits 1 to 3 after every 5 ± 1 EDs[x] until 20 ± 2 EDs at Visit 4, Visits 5 and 6 after each 10 ± 3 EDs, Visit 7 at 50-55 EDs, Visit 8 at 75 ± 5 EDs; and the Study Completion/Termination Visit for follow-up at 100-110 EDs. After each study visit following baseline, an IR will be determined except at Visit 1 (ED 5 ± 1),Visit 3 (ED 15 ± 1) and Visit 5 (ED 30 ± 3) when IR will be optional. If a subject is less than 3 years of age and has less than 2 joint bleeds, on-demand therapy with BAX 855 is permitted at a dose of 10-50 IU/kg, up to 80 IU/kg, depending on the severity of the bleeding. Prophylactic treatment consists of at least once weekly dosing of 25-50 IU/kg, which may be increased to 80 IU/kg, at the discretion of the investigator. Prophylactic dosing regimens of 3 or more doses weekly must be discussed with the sponsor. It must be initiated before the age

[ix] Commercial BAX 855 once approved
[x] ED visit window excludes the BAX 855 given during a given visit

of 3 years or if the subject has experienced a maximum of 2 joint bleeds, whichever occurs first, but can be started earlier.

If at any point during the study, a subject develops a high titer inhibitor (>5 BU/mL) confirmed at the central laboratory based on a second repeat blood sample drawn within 2 weeks of study site notification of an inhibitor, then the subject may enter Part B of the study for ITI therapy, provided informed consent is obtained.[32] If the subject has a confirmed low titer inhibitor (≥0.6 BU/mL but ≤5 BU/mL) that the principal investigator believes requires treatment with ITI or that cannot be managed with increased doses of BAX 855 or requires bypassing agents to treat bleedings, the subject may also enter Part B of the study. Also a low titer inhibitor has to be confirmed at the central laboratory based on a second repeat blood sample. In order to ensure timely availability of FVIII inhibitor results enabling the clinical management of the subject, results of the local laboratory may be used. However, if ITI has been initiated based on results of the local laboratory and a FVIII inhibitor is not confirmed by the central laboratory by the second repeat blood sample drawn within 2 weeks of study site notification of an inhibitor, the subject will discontinue ITI therapy, resume his original treatment regimen with BAX 855 and will transition back to Part A. Bypassing agents may be administered in Part A or Part B, based on local lab inhibitor results.

In the ITI portion of the study, subjects will complete a Screening and Baseline Visit which may coincide, Visit 1 at Week 2 ± 2 days, Visit 2 at Week 4 ± 2 days, and subsequent visits every month ±1 week, up to 33 months of total ITI treatment. The ITI therapy ranges between 50 IU/kg 3 x weekly to 100-200 IU/kg daily at the discretion of the investigator and according to the institution's standard of care.

An IR determination will be performed once 2 negative inhibitor titers within a two-month period have been obtained and will be repeated until IR is ≥66% of the initial IR value (by both one-stage and chromogenic methods). The IR should be performed after the longest time interval possible (preferably 48 hours) without undue interruption to the ITI therapy schedule.

If IR is ≥66% of the initial baseline value:

- ITI should be continued and IR with BAX 855 repeated within 2 months after a wash-out period of at least 84-96 h or the longest time interval possible without undue interruption to the ITI therapy schedule.
- If IR is again ≥66% of initial value, ITI therapy will be continued and a FVIII half-life determination performed within 2 months after a wash-out period of at least 84-96 h.
- When IR is ≥66% of the initial value and FVIII half-life ≥6 hours, ITI will be considered successful.

- If IR is ≥66% of the initial value and FVIII half-life <6 hours, ITI will be continued, and IR and half-life repeated at intervals no greater than 1 month apart.
- The high-dose ITI with BAX 855 will be gradually reduced over a 2-3-month period to a twice weekly prophylaxis:
  - 100 ± 5 IU/kg/day for the first 4 weeks, in case subject's ITI dose was 200 IU/kg/day;
  - then 50 ± 5 IU/kg/day for a further 4 weeks;
  - then 50 ± 5 IU/kg every second day for a further 4 weeks;
  - then 50 ± 5 IU/kg administered twice a week, adjusted as needed to maintain a FVIII trough level of 1%, for a further 3 months.
  - After the three-month follow-up period with twice weekly prophylaxis, a Completion/Termination Visit will be performed.
  - Subjects will be monitored for inhibitor recurrence prior to each dose adjustment and at the end of the three-month follow-up period using inhibitory and binding antibodies and FVIII recovery measurements. After this period, a Completion/Termination Visit will be performed (see Figure 2).
- Subjects receiving low dose ITI therapy with 3 x 50 IU/kg weekly will be transitioned to twice weekly 50 IU/kg, adjusted as needed to maintain a FVIII trough level of 1%, for a further 3 months. After this period, a Completion/Termination Visit will be performed at a time deemed feasible by the sponsor and investigator.

If BAX 855 IR is <66% of the initial baseline value:

- ITI therapy should be continued and BAX 855 IR repeated monthly after the longest time interval possible (preferably 48 hours), however, without undue interruption to the ITI therapy schedule until BAX 855 IR is ≥66% of the initial value.
- ITI should be continued and IR with BAX 855 repeated within 2 months after a wash-out period of at least 84-96 h or the longest time interval possible without undue interruption to the ITI therapy schedule.
- If IR is again ≥66% of initial value, the same procedures should be followed as described above.
- If IR is ≥66% of initial baseline IR, but FVIII half-life is <6 hours, ITI will be continued and IR and half-life repeated monthly.

- If FVIII half-life remains <6 hours and/or IR remains <66% of initial baseline value, these assessments should be repeated monthly until a maximum of 33 months of ITI has been provided and a Completion/Termination Visit will be performed.
- In case no baseline IR of Part A is available, the same procedures as described above should be performed. The baseline IR value of 66% is replaced by an IR indicative of an adequate clinical response which is an investigator and sponsor assessment based on pharmacokinetic parameters that permit effective prophylactic treatment of the study subject, including maintenance of FVIII levels above 1%.

A Completion/Termination Visit will also be performed in case of a partial success or failure after 33 months of ITI therapy or failure in terms of decline in the inhibitor titer of <20%, relative to the peak inhibitor titer, in any six-month period after the first 3 months of ITI therapy (in the absence of infection which in the opinion of the investigator could be expected to result in elevated inhibitor titers).

If a subject requires a surgical intervention during the main study (Part A), the subject's dosing of BAX 855 will be adjusted based on the IR (and half-life if available) and whether the procedure being performed is major or minor. Multiple surgeries are permitted in Part A; each will be recorded as a separate procedure. The surgery arm will not apply to the ITI part (Part B) of the study because if a subject requires a surgical intervention during this period, bypassing agents will be required. Therefore, subjects may remain in the study and undergo surgical interventions with bypass therapy, but there will be no specific protocol-defined regimens or assessments in Part B.

The study design is in compliance with the EMA/CHMP/BPWP/144533/2009 guidelines for the study of FVIII in hemophilia A.[10]

8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 8 years from study initiation (ie, first subject enrolled in Part A) to study completion (ie, last subject last visit in Part B). This consists of 5 years for Part A and 3.5 years for Part B. The recruitment period is expected to be 3 years.

The subject participation period is approximately 2 years from enrollment to subject completion (ie, last study visit), unless prematurely discontinued. Unless consent is withdrawn, subjects may be contacted by the investigator after the Study Completion Visit for up to 3 months for supplemental clinical information related to the study, if needed.

The duration of participation depends on the type of treatment regimen and the frequency of infusions. If the subject participates in Part B (ITI), there is an additional period of participation

of a maximum duration of 33 months, or until success or failure, whichever occurs first. In case of success, there will be an additional 2-3-month period for gradually reducing the high dose of BAX 855 to twice weekly prophylaxis treatment followed by a further three-month follow-up period with twice weekly prophylaxis.

8.3.1 Optional Extension of Access to Investigational Product

Optional extension of access to IP will be provided for qualifying subjects who completed their regular study period. Subjects who experience a clinical benefit from the IP, in the opinion of the investigator and confirmed by the sponsor, will be given the opportunity to continue receiving the IP under this protocol. Subjects who are granted extended access to the IP will continue to complete their electronic diaries, follow study procedures and return to the study site for unscheduled[xi] visits every 3 months. During these unscheduled visits, subjects will undergo the following procedures, as performed for Visit 8 (Section 20.2.1), at least 84-96 hours after the last infusion of BAX 855: physical exam, vital signs, FVIII assays, IR, CD4 (as needed), immunogenicity testing, assessment of bleeding episodes, review of subject diary, review of adverse events, concomitant medications and non-drug therapies. Drug accountability and distribution of IP will also be performed at these 3-month visits. Subjects will continue to complete the subject diary as during the regular study period.

Subjects on ITI will follow the monthly procedures for ITI, as specified in the protocol, until ITI success/failure has been established. If ITI is successful, subjects will undergo dose-tapering and then proceed to 3-month visits, as described for Part A. If ITI fails, subjects have the option to leave the study or further continue ITI adhering to the monthly follow-up visits and procedures.

8.3.2 Duration of Optional Extended Access to Investigational Product

Optional extended access can be terminated by sponsor when any of the following occurs:

- If the IP becomes available either commercially or via another access mechanism
- If marketing authorization in the country is rejected completely or for specific age groups (e.g., pediatrics)
- When the global trial is completed, in case marketing authorization in the country is not pursued by the sponsor
- If the subject or site does not adhere to the study procedures during the time of optional extended access.

[xi] "Unscheduled" in this context refers to visits to be performed during optional extended access following the regular study period.

At termination of optional extended access to IP, subjects will attend the study completion/termination visit.

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

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

8.4.2 Secondary Outcome Measures

8.4.2.1 Safety

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

8.4.2.2 Efficacy

- Annualized bleeding rate (ABR) for prophylactic and on-demand treatment
- Number of BAX 855 infusions per bleeding episode
- Overall hemostatic efficacy rating at 24 h after initiation of treatment and at resolution of bleed
- Weight-adjusted consumption of BAX 855 per month, per year and per event (prophylaxis, treatment of bleeding episode and surgery) and the number of infusions per month and per year
- Assessment of intra-, post- and perioperative hemostatic efficacy in case of surgery
- Intra- and postoperative blood loss in case of surgery

8.4.2.3 Pharmacokinetics

- IR at baseline and over time
- Half-life at baseline (optional). This is based on an abbreviated PK using 2 post-infusion timepoints: 15-30 minutes and 24–48 hours

8.4.2.4 Additional Outcome Measures for ITI

- **Primary**: The success rate of ITI therapy with BAX 855, success being defined as 1) a persistently negative inhibitor titer <0.6 BU (confirmed by central laboratory with second blood specimen obtained within 2 months); 2) a FVIII IR ≥66% of baseline value following a wash-out period of 84-96 h, and 3) a FVIII half-life of ≥6 hours. If no

baseline IR is available, the IR value is indicative of an adequate clinical response following a wash-out period of 84-96 h. An adequate clinical response is defined as pharmacokinetic parameters that permit effective prophylactic treatment of the study, including maintenance of FVIII levels above 1%.

- **Secondary**
  - The rate of partial success and failure of ITI with BAX 855.
    Partial success is defined after 33 months of ITI. Two of the following criteria must be met: 1) inhibitor titer <0.6 BU (confirmed by central laboratory with second blood specimen obtained within 2 months), 2) FVIII in vivo recovery ≥66% of baseline value (confirmed within a two-month period), and 3) FVIII half-life ≥6 hours. If no baseline IR is available, the IR value is indicative of an adequate clinical response following a wash-out period of 84-96 h. An adequate clinical response is defined as pharmacokinetic parameters that permit effective prophylactic treatment of the study, including maintenance of FVIII levels above 1%.

    Failure is defined as the failure to meet the criteria for success or partial success within 33 months of ITI therapy OR less than 20% reduction in inhibitor titer, relative to the peak inhibitor titer, over any six-month period after the first 3 months of treatment (in the absence of infection which in the opinion of the investigator could be expected to result in elevated inhibitor titers).
  - ABR during ITI
  - Weight-adjusted consumption of BAX 855 per month and per year for each ITI regimen employed
  - Catheter-related complications
  - Binding IgG and IgM antibodies to FVIII, PEG-FVIII, and PEG

8.4.3 Exploratory Outcomes Measure

[redacted]

8.5 Randomization and Blinding

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

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 anaphylaxis following exposure to BAX 855

The study may be terminated, or a study arm discontinued, 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. Other transfer sets may be employed as applicable to take into account the use of a central venous device. Four potencies of BAX 855 may be used, depending upon availability: 250, 500, 1,000 and 2,000 IU/vial. Potencies of BAX 855 with 750 IU/vial, 1500 IU/vial and 3000 IU/vial may be added when they are 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 instructions, 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 on vials in respective lots.

The actual dose administered should be based on the weight of the subject determined at the most recent study visit taking into account the allowable dose range.

PK assessment and IR determination

For the optional, abbreviated PK assessment and all IR determinations, only vials of the same lot should be used, preferably with a nominal potency of 500 IU. In order to ensure accurate dosing, whole vial doses should be administered and partial vials should be avoided. Vials of 250 IU potency may be used in subjects with low body weight to ensure a more precise dosing.

All other infusions (prophylaxis, treatment of bleeding episodes, perioperative management and ITI therapy)

Different lots and nominal potencies 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

BAX 855 will be administered at the Baseline Visit and at all study visits except for the following visits when both the IP infusion and IR determination are optional: Visit 1 (5 ± 1 EDs prior to visit), Visit 3 (15 ± 1 EDs prior to visit), and Visit 5 (30 ± 3 EDs prior to visit), (see Section 8.7.3.1). During the main study (Part A) subjects will receive either prophylaxis (see Section 8.7.3.2) and/or on-demand therapy (see Section 8.7.3.4) but prophylactic treatment must be initiated before the age of 3 years or once the subject has experienced 2 joint bleeds before the age of 3 years, whichever occurs first. If a subject takes part in Part B of the study, the subject will receive ITI therapy as described in Section 8.7.3.5.

In Parts A and B, IP will be dispensed at the study visits to provide sufficient treatment, at least until the next scheduled visit, or as appropriate. According to each study site´s standard of care and depending on the type of regimen, IP may also be dispensed more frequently.

8.7.3.1 BAX 855 Dosing for IR Assessment at Study Site

Part A: At baseline there should be a wash-out period of at least 72 hours after the last FVIII therapy, if applicable. For IR determination, after a pre-infusion blood draw within 30 minutes of infusion, it is recommended to infuse 50 ± 5 IU/kg of BAX 855, followed by a post-infusion blood draw at 15-30 minutes. In case of on-demand therapy or low dose prophylactic treatment, a lower dose for IR determination may be considered but should not be lower than 25 IU/kg. For post-baseline visits, whenever possible, there must be a minimum wash-out of 84-96 h after the last BAX 855 infusion; the timing of the BAX 855 infusion at the study site should be in accordance with the subject's prophylactic treatment regimen, if applicable.

Part B: In Part B, IR is assessed once a subject has 2 negative inhibitor titers within a two-month period and will be repeated until IR is ≥66% of the initial baseline IR value following the first BAX 855 infusion for IR determination in Part A (by both one-stage and chromogenic methods). The IR determination should always be performed after the longest time interval possible (preferably 48 hours) without undue interruption to the ITI therapy schedule. The recommended dose for IR determination in Part B is 50 ± 5 IU/kg, however, in order to avoid undue interruption of ITI therapy, the same ITI dose may be used for IR determination.

If the first IR is ≥66% of the initial baseline value:

- ITI should be continued and IR with BAX 855 repeated within 2 months (minimum 2 weeks) after a wash-out period of at least 84-96 h or the longest time interval possible without undue interruption to the ITI therapy schedule.
- If IR is again ≥66% of initial value, ITI therapy will be continued and a FVIII half-life determination performed within 2 months after a wash-out period of at least 84-96 h.
- When IR is ≥66% of initial value and FVIII half-life is ≥6 hours, ITI will be considered successful.
- The high-dose ITI with BAX 855 will be gradually reduced over a 2-3-month period to a twice weekly prophylaxis:
  - 100 ± 5 IU/kg/day for the first 4 weeks (± 1 week), in case subject's ITI therapy consisted of 200 IU/kg/day;
  - 50 ± 5 IU/kg/day for a further 4 weeks (± 1 week);
  - 50 ± 5 IU/kg every second day for a further 4 weeks (± 1 week);
  - 50 ± 5 IU/kg administered twice weekly, adjusted as needed to maintain a FVIII trough level of 1%, for a further 3 months.
  - After the three-month follow-up period with twice weekly prophylaxis, a Completion/Termination Visit will be performed.
  - Subjects will be monitored for inhibitor recurrence prior to each dose adjustment and at the end of the three-month follow-up period using FVIII binding and inhibitory antibodies and FVIII recovery measurements.
  - After this period, a Completion/Termination Visit will be performed.

- Subjects receiving low dose ITI therapy with 3 x 50 IU/kg weekly will be transitioned to twice weekly 50 IU/kg, adjusted as needed to maintain a FVIII trough level of 1%, for a further 3 months. After this period, a Completion/Termination Visit will be performed.

If BAX 855 IR is <66% of the initial baseline value:

- ITI therapy should be continued and BAX 855 IR repeated monthly after the longest time interval possible since last BAX 855 infusion (preferably 48 hours), however, without undue interruption to the ITI therapy schedule until BAX 855 IR is ≥66% of initial value.
- ITI should be continued and IR with BAX 855 repeated within 2 months after a wash-out period of at least 84-96 h since last BAX 855 infusion or the longest time interval possible without undue interruption to the ITI therapy schedule.
- If IR is again ≥66% of the initial value, the same procedures should be followed as described above.
- If IR remains <66% of the initial value, it should be repeated until a maximum of 33 months of ITI has been provided and a Completion/Termination Visit will be performed.
- If IR is confirmed to be ≥66% of initial baseline IR, but FVIII half-life is <6 hours, ITI will be continued and IR and half-life repeated monthly. If FVIII half-life remains <6 hours and/or IR remains <66% of the initial value, these assessments should be repeated monthly until a maximum of 33 months of ITI has been provided and a Completion/Termination Visit will be performed.

In case no initial baseline IR is available, the same procedures as described above should be performed, and an IR indicative of an adequate clinical response, as assessed by the investigator, will be used as the criterion. An adequate clinical response is defined as pharmacokinetic parameters that permit effective prophylactic treatment of the study subject, including maintenance of FVIII levels above 1%.

8.7.3.2 BAX 855 Dosing for PK Assessment

Part A: An optional abbreviated PK assessment to determine half-life can be performed at baseline, Visit 1, or Visit 2. The dosing for this PK is the same as the dosing for IR assessment consisting of 50 ± 5 IU/kg. If applicable, subjects should undergo a wash out period of at least 72 hours if they received prior FVIII treatment (84-96 hours if prior extended half-life FVIII treatment).

The blood draws for an abbreviated PK assessment include 1 pre-infusion, ie, within 30 minutes prior to infusion, followed by 2 post infusion blood draws at 15-30 minutes and 24-48 hours after infusion.

Part B: The same timepoints to determine FVIII half-life as described for Part A also apply for Part B. In Part B, FVIII half-life (PK) is determined (using 50 ± 5 IU/kg or the ITI dose) to assess the success of ITI. FVIII half-life will be assessed once a subject has 2 negative inhibitor titers within a two-month period and 2 FVIII IRs ≥66% of the initial baseline IR value in Part A within a two-month period, after a wash-out period of at least 84-96 hours. If IR is ≥66% but half-life is <6 hours, half-life determination will be repeated at intervals no greater than monthly. When IR is ≥66% of initial value and FVIII half-life ≥6 hours, ITI will be considered successful.

8.7.3.3 BAX 855 Individualized Prophylaxis Dosing

The prophylaxis dosing is at a dose of 25 to 50 IU/kg at least once weekly, up to 80 IU/kg, at the discretion of the investigator. Prophylaxis with 3 or more doses per week should be approved by the sponsor. Prophylactic treatment must be initiated before the age of 3 years or once the subject has experienced 2 joint bleeds, whichever occurs first.

8.7.3.3.1 Recommendations for BAX 855 Dose and/or Frequency Adjustments

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

- Two or more spontaneous (not trauma-related) bleeding episodes in the same target joint within any two-month period
- One or more spontaneous (not trauma-related) bleeding episodes in a non-target joint within any two-month period

The BAX 855 dosage may be increased gradually up to a maximum of 80 ± 5 IU/kg and/or the dosing frequency may be increased, if the subject continues to experience spontaneous breakthrough bleeding episodes or if, in judgment of the investigator, the subject's IR warrants higher doses. 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. The dose of 80 IU/kg is based on experience with ADVATE. Safety of PK doses of BAX 855 up to 60 IU/kg were evaluated in a Phase 1 study of BAX 855 (Study 261101) and in the pivotal Phase 2/3 study (Study 261201).

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

A target joint is defined as a single joint (ankles, knees, hips, or elbows) with ≥3 spontaneous bleeding episodes in any consecutive six-month period.[32] The joint is no longer considered a target joint when there have been ≤2 bleeds into the joint within a consecutive 12 month period.[32] For definitions of joint and muscle bleeding, see Section 20.4.

8.7.3.4 BAX 855 On-demand Dosing for Treatment of Bleeding Episodes

Part A: The on-demand treatment is at a dose of 10-80 IU/kg depending on the severity of the bleeding episode. On-demand therapy is only available for subjects up to the age of 3 years and as long as they have not experienced 2 joint bleeds. However, they must be transitioned to prophylaxis before they reach the age of 3 years or they have experienced 2 joint bleeds before this age limit.

BAX 855 will be used for the treatment of bleeding episodes according to the guidelines outlined in Table 1. The subject or their caregiver will rate the severity (mild, moderate, or severe) of the bleeding episode and will rate the overall treatment response at 24 ± 2 hours and at resolution of bleed. A 4-point efficacy rating scale (see Table 2 in Section 11.1.2) will be used to assess the efficacy of BAX 855 treatment. Since efficacy rating is based to a large degree on cessation of pain, the investigator/legal representative shall, in particular in case of injury-related bleeding into one or more than one location, take the injury-related symptoms into consideration when performing the efficacy rating at resolution of the bleed.

As per Table 1, 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.

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.

Table 1
BAX 855 Treatment Guidelines for Bleeding Episodes

Severity and Type of Bleeding Episode	FVIII Level Required (%)	*Suggested Dose* 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 hours. Duration: at least 1 day, until the bleeding episode is resolved or healing is achieved
Moderate Moderate bleeding into muscles, bleeding into the oral cavity, definite/more extensive hemarthroses, and known trauma	30 to 60%	*15 to 30 ± 5 IU/kg* Repeat infusions every 12 to 24 hours for 3 days or more until the pain and acute disability/incapacity are resolved
Major/life-threatening (severe) 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 hours 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 average recovery of 2 [IU/dL]/[IU/kg] for FVIII products should be used and the required units are 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.

Part B: Rescue therapy for patients who experience acute bleeding episodes during ITI will be treated with the institution's mandated standard of care, which is normally a bypassing agent such as FEIBA (Anti-Inhibitor Coagulant Complex) or Novoseven (recombinant factor VIIa). Bypassing agents are not IPs in the context of this study.

8.7.3.5 BAX 855 Dosing During Surgical, Dental or Invasive Procedures

In Part A, the dose and frequency of BAX 855 administered during surgical, dental or invasive procedures will be individualized based on the subject's BAX 855 IR and half-life, if available, to obtain the target level required for the type of the surgery, dental or other invasive procedure being performed. In general, for major surgery initial FVIII target levels in plasma should be ≥80-100% of normal FVIII level, whereas for minor surgery target FVIII levels should be ≥30-60%. For definitions of minor and major surgeries, see Section 21.2. For further details of dosing and dosing schedule in case of major surgeries, see Section 22.

Part B: Should a patient undergoing ITI require a surgical procedure, the type of bypassing agent and the perioperative management (dose, frequency and duration) will be at the discretion of the investigator according to the institution's standard of care.

8.7.3.6 BAX 855 ITI

The dosing schedule for ITI therapy with BAX 855 is either a high-dose regimen of 100-200 IU/kg daily or a low-dose regimen of 50 IU/kg 3 x weekly and is at the discretion of the investigator. Before the start of ITI therapy, the sponsor should be notified about the planned therapy during screening.

To monitor the outcome of ITI, subjects will be evaluated monthly for FVIII inhibitors and binding antibodies to FVIII, BAX 855 and PEG. Blood draws will be performed without undue interruption of ITI therapy. Once a subject has 2 negative inhibitor titers within a two-month period, IR should be assessed (see Section 8.7.3.1 for the description of IR determination during ITI therapy). ITI therapy will last until the success criteria are met or 33 months, whichever occurs first. Also, in case a 20% reduction in inhibitor titer, relative to the peak inhibitor titer, is not observed over any six-month period after the first 3 months of treatment (in the absence of infection which in the opinion of the investigator could be expected to result in elevated inhibitor titers), ITI therapy is considered a failure and a Completion/Termination Visit will be performed at a time deemed feasible by the investigator and sponsor.

Transitioning to twice weekly prophylaxis after successful ITI

Subjects receiving high-dose ITI therapy:
Dose will be reduced to the standard twice weekly prophylaxis dose regimen over 2-3 months according to the following schedule, starting when the patient is judged to be inhibitor-free and criteria for success are met:

- 100 ± 5 IU/kg/day for the first 4 weeks, if starting at 200 IU/kg/day; then
- 50 ± 5 IU/kg/day for a further 4 weeks; then
- 50 ± 5 IU/kg every second day for a further 4 weeks; then

- 50 ± 5 IU/kg administered twice a week, adjusted as needed to maintain a FVIII trough level of 1%, for a further 3 months.

Subjects will be monitored for inhibitor recurrence prior to each dose adjustment and at the end of the 2-3-month follow-up period using inhibitory and binding antibodies to FVIII and FVIII recovery measurements (see also Figure 2). This will coincide with the Completion/Termination Visit.

Subjects receiving low dose ITI therapy with 3 x 50 IU/kg weekly:
Starting when the patient is judged to be inhibitor-free and criteria for success are met, the subject will be transitioned to twice weekly 50 IU/kg, adjusted as needed to maintain a FVIII trough level of 1%, for a further 3 months. After this period, a Completion/Termination Visit will be performed.

8.7.4 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), and the subject must return at each visit all used and unused IP vials. 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 17.2. The use of subject diaries is described in Section 10.5.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

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

1. Subject is <6 years old at the time of screening
2. Subject is previously untreated with <3 EDs to ADVATE, BAX 855 or plasma transfusion at any time prior to screening
3. Subject has severe hemophilia A (FVIII <1%) as determined by the central laboratory, or a historical FVIII level <1% as determined at any local laboratory, optionally supported by an additional FVIII gene mutation consistent with severe hemophilia A
4. Subject is immune competent with a CD4+ count >200 cells/mm3, as confirmed by the central laboratory at screening
5. Parent or legally authorized representative is willing and able to comply with the requirements of the protocol

Additional inclusion criteria for Part B (ITI)

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

9.2 Exclusion Criteria

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

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

4. Subject has been previously treated with any type of FVIII concentrate other than ADVATE or BAX 855[xii], or was administered ADVATE, BAX 855 or plasma transfusion for ≥3 EDs at any time prior to screening
5. Subject receives >2 EDs of ADVATE in total during the periods prior to enrollment and during the screening period, until the baseline infusion.
6. The subject's weight is anticipated to be <5 kg at the baseline visit[xiii]
7. Subject's platelet count is <100,000/mL
8. Subject has known hypersensitivity towards mouse or hamster proteins, PEG or Tween 80
9. Subject has severe chronic hepatic dysfunction [eg, >5 times upper limit of normal alanine aminotransferase (ALT), aspartate aminotransferase (AST), or a documented INR >1.5] in his medical history or at the time of screening
10. Subject has severe renal impairment (serum creatinine >1.5 times the upper limit of normal)
11. 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
12. 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[xiv]
13. 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
14. Parent or legally authorized representative has a medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance
15. Parent, legally authorized representative or subject are a member of the team conducting this study or is in a dependent relationship with one of the study team members. Dependent relationships include close relatives (ie, children, partner/spouse, siblings, parents) as well as employees of the investigator or site personnel conducting the study.

[xii] BAX 855 refers to commercial BAX 855 in those countries where licensed at the time the study is performed.
[xiii] If a subject is close to weighing 5 kg at screening and will have reached a weight of at least 5 kg at the baseline visit, the subject is eligible for participation.
[xiv] The use of systemic immunomodulating drugs, eg, with anti-CD20 chimeric monoclonal antibody rituximab, as part of ITI therapy with BAX 855 is permitted.

Additional exclusion criteria for Part B (ITI)

1. Spontaneous disappearance of the inhibitor prior to ITI
2. FVIII inhibitor titer ≥0.6 BU is not confirmed by a second new blood sample and determined at the central laboratory
3. Inability or unwillingness to comply with the protocol

9.3 Withdrawal and Discontinuation

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

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

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

- The subject experiences a severe anaphylactic reaction to BAX 855.
- The subject requires therapy with another PEGylated product (eg, PEG- interferon).
- The subject frequently misses administration of IP (eg, misses more than 30% of planned prophylactic doses within any three-month period).
- The subject/legal representative is non-compliant with study procedures, in the opinion of the investigator.
- The subject is planned to undergo ITI therapy with a FVIII concentrate other than BAX 855.
- In case of ITI: The subject/legal representative is non-compliant with ITI therapy.

The subject does not demonstrate a 20% reduction in inhibitor titer, relative to the peak inhibitor titer, over any six-month period after the first 3 months of ITI therapy (in the absence of infection which in the opinion of the investigator could be expected to result in elevated inhibitor titers).

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

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

10.2 Subject Identification Code

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

10.3 Screening and Study Visits

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. Screening is defined as first blood draw, including laboratory evaluations.

If a subject does not satisfy all screening criteria, the same subject may be rescreened at a later date. A partial or full rescreening may also become necessary at the discretion of the investigator or sponsor. For the purpose of analysis, only the data from the most recent screening visit will be used for screening assessments that were repeated during rescreening. If a subject is rescreened, the End of Study CRF should be completed, and a new informed consent form, new SIC and new CRF are required for that subject. Blood draws for laboratory tests may be staggered over the entire screening period of 45 days after the screening visit. In such a case, blood draws for assays requiring the longest turn-around-time will be taken first, eg, FVIII activity, inhibitory and binding antibodies to FVIII, PEG and BAX 855 (for further details see laboratory manual). If the timeframe of 45 days is exceeded, then some screening assessments may be repeated at the discretion of the sponsor, and the subject will be assigned a new SIC. Exemptions may be provided if the 45 days for screening is exceeded due to administrative reasons after sponsor approval.

Treatment with ADVATE up to 2 EDs in total in the combined period prior to screening and during screening is allowed. Bleeding episode treatment may utilize commercial Adynovate/Adynovi during the screening period. Plasma transfusion during the screening period will necessitate that the subject be partially or fully rescreened, at the discretion of the sponsor.

The overall study design is illustrated in Figure 1. Details on the procedures to be performed at each study visit, including screening, can be found in Supplement 20.1 Detailed Flow Diagram of Study Procedures, Supplement 20.3 Schedule of Study Procedures and Assessments and Clinical Laboratory Assessments for Part A, and Supplement 20.4 with the corresponding schedules for Part B.

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 (eg, PEG-interferon)
  - Any investigational drug, biologic, or device

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

Part A: The use of any FVIII concentrate other than BAX 855 during the course of the study following the first baseline BAX 855 infusion will result in the immediate withdrawal of the subject[xv]. Every effort should be made to have the Completion/Termination Visit performed.

The use of commercial bypassing agents is permitted in Part A, prior to enrollment in Part B, if local lab results indicate the presence of an inhibitor.

Part B: The use of commercial bypassing agents for perioperative management and the prevention and/or control of bleeding episodes during ITI therapy is permitted. Also, bypassing agents may be employed after detection of a high-titer inhibitor until initiation of ITI therapy (eg, until FVIII inhibitor is <5 or <10 BU). The use of systemic immunomodulating drugs (eg, anti-CD20 chimeric monoclonal antibody rituximab) as part of ITI therapy with BAX 855 is permitted.

[xv] The exceptional use of commercial ADVATE may be permitted by the sponsor for a short period of time for administrative reasons. ADVATE is not IP in this context.

The following medications and non-drug therapies are permitted before study entry and during the course of the study (Parts A and B):

- Medications:
  - Hemostatic agents, such as tranexamic acid, are permitted, as indicated by the subject's treating physician, to treat mucosal bleeding during the study or during a surgical or other invasive procedure
  - 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
  - **Immunization:**
    - The concurrent administration of a vaccine and BAX 855 at site visits should be avoided.
    - If possible, intramuscular vaccination should be replaced by subcutaneous administration.
    - Vaccinations 1 month prior to and during the study should be recorded as concomitant medications
  - Bypassing agents, eg, Factor Eight Inhibitor Bypassing Activity (FEIBA), or rFVIIa in Part B, or in Part A for a clinically suspected inhibitor. Bypassing agents are not IPs in the context of this study.
- Non-drug therapies:
  - Any non-drug therapy (eg, physiotherapy) deemed necessary by the subject's physician to treat or prevent any medical condition

10.5 Subject Diary

An electronic subject diary (eDiary)[xvi] will be provided to each subject/legal representative at the respective Screening Visit to record the following information during Parts A and B:

1. Infusion record for BAX 855
2. Infusion record for bypassing agents in Part B (if applicable)

[xvi] The transient use of a paper diary may become necessary during the course of the study for administrative reasons or in the event that eDiary cannot be made available in subject's native language.

3. Details of bleeding episodes and response to treatment
4. Untoward events

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

- Location of bleed, eg, joint, soft tissue, muscle, body cavity, intracranial, other.
- Type of bleed, ie, spontaneous (definitely no injury/trauma), injury (definitely due to injury/trauma).
- Severity of bleed, eg, minor, moderate, major/severe (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.
- In Part A only: Overall clinical efficacy rating according to the rating scale as described in Table 2 at 24 (± 2) hours after initiation of treatment and at resolution of bleed (see Table 2, Section 11.3 Hemostatic Efficacy Rating for Treatment of Bleeding Episodes)

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic format at the start of Part A and at the start of Part B, if applicable, and remain with the subject for the duration of that part of the study. The subject will bring the diary to each study visit. The investigator will review the diary for completeness and request missing information at each visit and in a timely manner. Untoward events recorded in the diary will be reported as AEs according to the investigator's discretion and clinical judgment.

Subject entries in the diary will serve as source records. During study participation the investigator has access to electronic subject diary data and must review and correct (if applicable) electronic diary data every 2 weeks. Any site changes/corrections to subject diary data will be supported by source documentation.

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.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures according with the protocol (with or without protocol deviations). Prior to subject study completion, the site must notify the sponsor (eg clinical research associate) of planned completion visit and obtain sponsor approval.

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

Every effort will be made to have discontinued subjects complete the study Completion/ Termination Visit. If the Completion/Termination Visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the Completion/ Termination Visit. If a subject terminates participation in the study and does not return for the Completion/Termination Visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the Termination Visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.1 Detailed Flow Diagram of Study Procedures, Supplement 20.3 Schedule of Study Procedures and Assessments and Clinical Laboratory Assessments for Part A, and Supplement 20.4 with the corresponding schedules for Part B.

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 by site staff, electronically every 2 weeks, in person at every patient visit, 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 (eg, 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 Supplement 21.1. Bleeds occurring at the same anatomical location (eg, right knee) with the same etiology (ie, spontaneous vs. injury) within 72 h of onset of the first bleed will be considered a single bleed.[32] 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. Bleeding occurring at multiple locations related to the same injury (eg, knee and ankle bleeds following a fall) will be counted as a single bleeding episode.

Only bleeding episodes treated with BAX 855 will be evaluated for hemostatic efficacy as described in the following sections, whereas bleeding episodes requiring bypassing agents in Part B will not be evaluated for hemostatic efficacy.

11.1.1 Number of BAX 855 Infusions Needed for the Treatment of Bleeding Episodes (Part A)

The number of BAX 855 infusions needed for each bleeding episode 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, eg, due to vascular access issues, and must be re-started, it will be recorded as 1 infusion. If an infusion is terminated for any reason prior to completion of infusion and not restarted, it will be recorded as an infusion; reasons for not completing the infusion will be recorded.

11.1.2 Hemostatic Efficacy Rating for Treatment of Bleeding Episodes (Part A)

The subject or their caregiver will rate the severity (minor, moderate, or major/life-threatening) of the bleeding episode and will rate the overall treatment response at 24 ± 2 hours after the initiation of treatment, and at bleeding episode resolution, 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 24 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.

Table 2
Efficacy Rating Scale for Treatment of Bleeding Episodes

Excellent	Full relief of pain and cessation of objective signs of bleeding (eg, swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	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. The investigator will either confirm the efficacy rating or record an updated efficacy rating with appropriate source documentation justifying the change:

- 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 1 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 1 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 adequately in the subject's electronic diary and integrated in the eCRF.

11.2 Weight-adjusted Consumption of BAX 855 in Part A

Weight-adjusted consumption of BAX 855 will be determined based upon the record in subjects' diaries of the actual amount of BAX 855 infused, indication (treatment of bleeding episode, prophylaxis) and the subject's weight, as measured in the clinic.

11.3 Perioperative Management in Part A

11.3.1 Intra-, Post-, and Perioperative Hemostatic Efficacy

The hemostatic efficacy will be assessed during (Table 3) and after (Table 4) any surgical or invasive procedures, and overall as a perioperative assessment (Table 5).

Table 3
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**	**Score**
Excellent	Intraoperative blood loss was less than or equal to that expected (≤100%)	3
Good	Intraoperative blood loss was up to 50% more than expected (101-150%)	2
Fair	Intraoperative blood loss was more than 50% of that expected (>150%)	1
None	Uncontrolled hemorrhage that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy	0

Table 4
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**	**Score**
Excellent	Postoperative blood loss was less than or equal to (≤100%) that expected	3
Good	Postoperative blood loss was up to 50% more (101-150%) than expected	2
Fair	Postoperative blood loss was more than 50% (>150%) of that expected	1
None	Significant postoperative bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy	0

Table 5
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**	**Score**
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	3
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	2
Fair	Perioperative blood loss was more than 50% of that expected (>150%) Required blood components transfusions were greater than that expected	1
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	0

11.3.2 Intra- and Postoperative Blood Loss

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

Prior to each 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 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. Post-operatively, 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".

11.4 ITI Therapy (Part B)

11.4.1 Definition of Success, Partial Success and Failure

Success is defined as 1) a persistently negative inhibitor titer <0.6 BU, 2) FVIII IR ≥66% of the baseline value following a wash-out period of 84-96 h, and 3) a FVIII half-life of ≥6 hours. In case no baseline IR is available, an IR value indicative of an adequate clinical response following a wash-out period of 84-96 h will be used for the definition of success. An adequate clinical response is defined as pharmacokinetic parameters that permit effective prophylactic treatment of the study subject, including maintenance of FVIII levels above 1%.

Partial success is defined after 33 months of ITI. Two of the following criteria must be met: 1) inhibitor titer <0.6 BU (confirmed by a central laboratory with a second blood specimen obtained within 2 months), 2) FVIII in vivo recovery ≥66% of baseline value (confirmed within a two-month period), and 3) FVIII half-life ≥6 hours. If no baseline IR is available, the IR value is indicative of an adequate clinical response following a wash-out period of 84-96 h. An adequate clinical response is defined as pharmacokinetic parameters that permit effective prophylactic treatment of the study, including maintenance of FVIII levels above 1%.

Failure is defined as the failure to meet the criteria for success or partial success within 33 months of ITI therapy OR less than 20% reduction in inhibitor titer, relative to the peak inhibitor titer, over any six-month period after the first 3 months of treatment (in the absence of infection which in the opinion of the investigator could be expected to result in elevated inhibitor titers).

11.4.2 Weight-adjusted Consumption of BAX 855 in Part B

The weight adjusted consumption of BAX 855 will be evaluated per month and per year for each ITI regimen employed.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

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

12.1.1.1 Serious Adverse Event

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

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (ie, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
  - Development of a confirmed inhibitory antibody based on a second blood draw to FVIII within 2 weeks of study site notification of an inhibitor determined at the central laboratory with an inhibitor level ≥0.6 BU/mL using the Nijmegen modification of the Bethesda assay
  - 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)
- Thromboembolic events (e.g., stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism)

For the purpose of this study:

- Any hospitalization due to a planned surgical intervention or the placement or planned removal of a CVD is not considered an SAE. However, any planned surgery becoming necessary due to a worsening condition of the subject during the study period constitutes an SAE.

12.1.1.2 Non-Serious Adverse Event

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

12.1.1.3 Unexpected Adverse Events

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

For the purposes of this study, all AEs, including unexpected AEs, experienced by a subject undergoing study-related procedure(s) will be recorded on the AE CRF.

12.1.1.4 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.

12.1.2 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:

- Occurrence of bleeding episodes: Bleeding episodes are part of the disease. Treatment and prevention of bleeding episodes are secondary efficacy outcome measures.
- Hospitalizations for planned medical or surgical procedures, eg, placement of a central venous line. In case hospitalizations become necessary due to a worsening condition of the subject, it will constitute an AE.

All other AEs from the first IP exposure until study completion/discontinuation date 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 12.1). Each AE will be evaluated by the investigator for:

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

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until the study Completion/ Termination Visit; the follow-up information will be documented in the CRF. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (ie, the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including overdosing [exceeds maximum recommended dose by 20%], underdosing [>10% below the minimum recommended dose], abuse, and withdrawal, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

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

12.1.2.1 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.

12.1.2.2 Causality

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

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not associated with the IP (ie, does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP

- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive rechallenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 96 h after IP infusion, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.1.3 Medical Device Safety Reporting

The IP kit contains the BAXJECT device. All Serious Injuries (SI) and Unexpected Adverse Device Events (UADE) must be reported. Serious injury is defined as:

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

12.2 Urgent Safety Measures

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

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

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent

immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committee is notified of the urgent measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

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

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

12.4 Non-Medical Complaints

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

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

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

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) or surgery and start and end dates, if known:

eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All medications taken including immunization 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.

In addition, any prior use of the following products (name of drug, indication, and dates of use) at any time in the past will be recorded on the eCRF:

- Any PEGylated medication
- Plasma, cryoprecipitate, any type of FVIII concentrate
- Any kind of blood-transfusion such as packed red blood cells (PRBC), platelets or plasma

12.6 Physical Examinations

At screening and subsequent study visits (as described in Section 20.1), 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 study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.4), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.7 Clinical Laboratory Parameters

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

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 Supplement 20.3, Table 7 for Part A and in Supplement 20.4, Table 9 for Part B.

12.7.1 Immunogenicity

The immunogenicity assessments are:

- Inhibitory antibodies to FVIII. A subject will be defined as positive for inhibitor development with a titer of ≥0.6 BU/mL using the Nijmegen modification of the Bethesda assay. Any positive titers should be confirmed with a second repeat sample drawn within 2 weeks of study site notification of an inhibitor.
- Binding IgG and IgM antibodies to FVIII, PEG-FVIII and PEG: Both IgG and IgM binding antibodies will be analyzed, using a multi-tiered approach consisting of screening assay, titer determination and confirmation of specificity. If binding IgG antibodies with confirmed specificity against FVIII or PEG-FVIII are present, IgG subclasses and IgA will be determined. [redacted]
- Immunogenicity will be tested in both Part A and Part B of the study. If the subject has received an infusion of a FVIII product prior to baseline there must be a minimum wash-out of at least 72 hours, and post-baseline there must be a minimum wash-out of at least 84–96 h after the last BAX 855 infusion. Blood draws for immunogenicity assessments have to be performed within the 30 minutes before the BAX 855 infusion is administered at the study site. In part B, the longest permissible wash-out period should be observed, however, without undue interruption of ITI therapy.
- FVIII inhibitory antibodies are determined at the central laboratory. However, in order to ensure the timely availability of FVIII inhibitor results, the clinical management of the subject may be based on results generated at the local laboratory. An additional blood sample needs to be drawn for testing at the central laboratory to confirm the result determined at the local laboratory.

In case of a severe hypersensitivity reaction, an additional blood sample has to be drawn to test for the presence of IgE antibodies against FVIII and PEG.

12.7.2 Pharmacokinetics

If the subject has a central or peripheral venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples. 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, and heparin or anticoagulant flushes should be avoided prior to blood sampling, when feasible. At least 5 mL of whole blood must be collected and discarded prior to obtaining the blood sample.

12.7.2.1 Incremental Recovery

The FVIII assays are: one-stage clotting FVIII activity and FVIII chromogenic activity.

In Part A, BAX 855 is administered for the determination of FVIII IR at the study site at baseline and every study visit other than study visits 5 ± 1 EDs, 15 ± 1 EDs and 30 ± 3 EDs, when IR determination is optional. If the subject has received an infusion of a FVIII product prior to baseline, there must be a minimum wash-out of at least 72 hours, and post-baseline there must be a minimum wash-out of at least 84-96 hours after the last BAX 855 infusion. A pre-infusion blood sample is drawn within 30 minutes before the infusion, then 50 ± 5 IU/kg of BAX 855 is infused, followed by a post-infusion blood-draw at 15-30 minutes. In case of low dose prophylactic treatment or on-demand treatment, a lower dose for IR determination may be considered but should not be lower than 25 IU/kg.

In Part B, IR is assessed once a subject has 2 negative inhibitor titers within a two-month period (minimum 3 weeks apart) and will be repeated until IR is ≥66% of the initial baseline IR value in Part A. The IR should be performed after the longest time interval possible (preferably 48 hours) without undue interruption to the ITI therapy schedule. The dose for IR determination in Part B is 50 ± 5 IU/kg, however, in order to avoid undue interruption of ITI therapy, the same ITI dose may be used for IR determination. If the IR is ≥66% of the initial baseline value, ITI should be continued and IR determination with BAX 855 repeated within 2 months after a wash-out period of at least 84-96 h or the longest time interval possible without undue interruption to the ITI therapy schedule. If IR is again ≥66% of initial value, ITI therapy will be continued and a FVIII half-life determination performed within 2 months , after a wash-out period of at least 84-96 hours. When IR is ≥66% of initial value and FVIII half-life ≥6 hours, ITI will be considered successful.

Once success is confirmed, the high-dose ITI with BAX 855 will be gradually reduced over a 2-3-month period to a twice weekly prophylaxis as described in Section 8.7.3.6 BAX 855 ITI.

Prior to each dose reduction, FVIII binding and inhibitory antibodies and a FVIII IR will be determined. If a subject experiences a confirmed increase in FVIII inhibitor titer (>0.6 BU) and/or decrease in the IR (<66% of the initial baseline value) at the planned time of dose adjustment to the next lower dose/frequency level, the following procedures will be followed (see also Figure 2):

- For 2 months the subject will transition back to the next higher dose/frequency level, eg, the subject will be restarted on 200 IU/kg/day if the inhibitor titer increase and/or IR decrease occurred after 4 weeks of 100 IU/kg/day.
- After 2 months, FVIII binding and inhibitory antibodies and IR will be re-assessed and if both parameters have normalized, the subject can continue the dose reduction schedule as

described in Section 8.7.3.6 BAX 855 ITI followed by the Completion/Termination Visit after a three-month follow-up period with twice weekly prophylaxis has been completed.

- If the FVIII inhibitor titer remains >0.6 BU and/or IR <66% after 2 months of receiving the higher dose/frequency, then the subject should continue with the same dose/frequency level for an additional 2 months.
- The above process can be repeated one more time. If FVIII inhibitor and FVIII IR both are normalized, the same procedures and dose reduction schedule as described above apply.
- If the FVIII inhibitor titer continues to be >0.6 BU and/or IR <66%, there are 2 options:
  - A Completion/Termination Visit is performed.
  - The subject can be switched to a low dose ITI therapy consisting of 50 IU/kg 3 times weekly for 3 months. Binding and inhibitory antibodies and FVIII IR should be assessed on a monthly basis and if the inhibitor titer and IR are normalized, the subject should proceed to twice weekly prophylaxis for 3 months followed by the Completion/Termination Visit. If either FVIII inhibitors or FVIII IR is not normalized after 3 months of low dose ITI therapy, a Completion/Termination Visit should be performed.

If the BAX 855 IR is <66% of the initial value, ITI therapy should be continued and BAX 855 IR repeated monthly after the longest time interval possible (preferably 48 hours), however, without undue interruption to the ITI therapy schedule until BAX 855 IR is ≥66% of initial value. ITI should be continued and IR with BAX 855 repeated within 2 months after a wash-out period of at least 84-96 h or the longest time interval possible without undue interruption to the ITI therapy schedule. If IR is again ≥66% of initial value, ITI therapy will be continued and a FVIII half-life determination performed within 2 months after a wash-out period of at least 84-96 h. When IR remains ≥66% of initial value and FVIII half-life is ≥6 hours, ITI will be considered successful and the high-dose of BAX 855 will be gradually reduced over a 2-3-month period to a twice weekly prophylaxis as described in Section 8.7.3.6 BAX 855 ITI. After a further three-month follow-up period with twice weekly prophylaxis, a Completion/Termination Visit will be performed. For low-dose ITI, once success criteria have been met, the prophylactic regimen will be transitioned as in Section 8.7.3.6 BAX 855 ITI.

If FVIII half-life is <6 hours, ITI will be continued and IR and half-life repeated monthly. If FVIII half-life remains <6 hours and/or IR remains <66% of initial value, these assessments should be repeated monthly until a maximum of 33 months of ITI has been provided and the Completion/Termination Visit will be performed.

In case no initial baseline IR of Part A is available, the same procedures as described above should be performed. The baseline IR value of 66% is replaced by an IR indicative of an adequate clinical response which is defined as pharmacokinetic parameters that permit effective prophylactic treatment of the study subject, including maintenance of FVIII levels above 1%.

12.7.2.2 FVIII Half-life

The abbreviated PK to determine FVIII half-life is an optional assessment that can be performed at baseline, Visit 1, or Visit 2. The dosing for this PK is the same as the dosing for IR assessment consisting of 50 ± 5 IU/kg. If the subject has received an infusion of a FVIII product prior to baseline there must be a minimum wash-out of at least 72 hours. A blood sample will be drawn within 30 ± 5 minutes before, and 15-30 minutes and 24-48 hours after BAX 855 infusion. If no abbreviated PK is performed, at least a 15-30 minutes post-infusion blood draw for the determination of the initial FVIII recovery will be taken for the Baseline Visit.

In Part B, FVIII half-life is determined to assess the success of ITI. FVIII half-life will be assessed with a dose of 50 ± 5 IU/kg or the current prophylactic dose, once a subject has had 2 negative inhibitor titers within a two-month period and 2 IRs ≥66% of the initial baseline IR value in Part A within 2 months after a wash-out period of at least 84-96 hours. ITI therapy will be continued and a FVIII half-life determination performed within 2 months after a wash-out period of at least 84-96 hours. When IR is ≥66% of the initial value and FVIII half-life ≥6 hours, ITI will be considered successful (see Section 12.7.2.1). If the 2 IRs are >66% but FVIII half-life is <6 hours, the half-life determination is to be repeated monthly. The same post-infusion blood sampling time-points as described for Part A apply also for Part B.

12.7.3 Hematology and Clinical Chemistry

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

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

In Part A, blood will be obtained for assessment of hematology at screening, and then every 3 months after Visit 5.

In Part A, blood will be obtained for assessment of clinical chemistry parameters at screening/baseline, at Visit 5 after 30 ± 3 EDs, at Visit 7 after 50-55 EDs, and at the Study Completion/Termination Visit for follow-up at 100-110 EDs.

In Part B, the sampling times for clinical chemistry and hematology are at screening, every 3 months and at Completion/Termination.

Hematology will be performed on ethylene diamine tetra acetic acid (EDTA)-anticoagulated whole blood and clinical chemistry assessments will be performed on serum, at the central laboratory.

12.7.4 Other Laboratory Tests

12.7.4.1 CD4 Count

The CD4 count is analyzed to determine subject's eligibility at Screening; thereafter every year.

12.7.4.2 Genetics and HLA-genotype

FVIII gene mutation analysis and human leukocyte antigen (HLA) genotype will be analyzed at screening, or at a later visit, if necessary. 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.

12.7.4.3 [redacted]

[redacted]

12.7.5 Assessment of Laboratory Values

12.7.5.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each laboratory value will be recorded on the eCRF. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 12.1, and record the sign, symptom, or medical diagnosis on the AE CRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.4), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, ie because it is due to a preexisting disease, due to a lab error, or due to another issue that will be specified.

Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.7.6 Biobanking

Backup samples should be taken and stored appropriately for additional analysis, if necessary. These samples may be used for re-testing, further evaluation of an AE, or follow-up of other test results. The following samples are planned:

- Backup samples for testing of inhibitory antibodies to FVIII and binding IgG and IgM antibodies to FVIII, PEG-FVIII, and PEG.
- Optional backup samples for FVIII testing will be taken at each study visit.

Backup samples that remain after study testing is done may be stored and used for additional testing (eg, further evaluation of an abnormal test or an AE) and further assay optimization. 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.

12.8 Vital Signs

Vital signs will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (in or cm) will be collected at Screening and weight (lb or kg) will also be collected at Screening and at all pre-infusion assessments. Also, height will be measured every 6 months.

Vital signs will be measured at screening and within 15 minutes before and 15 to 30 minutes after administration of IP, at each study visit except for Visits 1, 3 and 5 (ie, at Baseline Visit, Visit 2 after 10 ± 1 EDs, Visit 4 after 20 ± 2 EDs, Visit 6 after 40 ± 3 EDs, Visit 7 at 50-55 EDs, and Visit 8 at 75 ± 5 EDs), and at study Completion/Termination at 100-110 EDs. Blood pressure will be measured when subjects are in the supine position.

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

13. STATISTICS

13.1 Sample Size and Power Calculations

The sample size of 100 subjects followed for 100 EDs originates from EMA/CHMP/BPWP/144533/2009[10]; it is not based on statistical considerations.

13.2 Datasets and Analysis Cohorts

13.2.1 Safety Analysis Dataset

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.

13.2.2 Prophylaxis Analysis Dataset (PAS)

The prophylaxis analysis dataset will comprise all subjects who were on BAX 855 prophylaxis for at least 1 infusion.

13.2.3 Hemostatic Efficacy Dataset (HEAS)

The hemostatic efficacy analysis dataset will comprise all subjects who were treated for one or more bleed with BAX 855.

13.2.4 Surgery Analysis Dataset (SUAS)

The surgery analysis dataset will comprise all subjects who were treated with BAX 855 for one or more surgery in the context of the study.

13.2.5 ITI Analysis Dataset (IAS)

The ITI analysis dataset will comprise all subjects who were treated with BAX 855 for ITI in the context of the study.

13.3 Handling of Missing, Unused, and Spurious Data

Missing data will not be imputed in general. However, 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".

13.4 Methods of Analysis

13.4.1 Primary Outcome Measure

Incidence of FVIII inhibitor development

The Clopper-Pearson exact 95% confidence interval will be computed for the proportion of subjects who developed FVIII inhibitors during the study.

The set of subjects to be analyzed includes all subjects who developed an inhibitor (at any time) confirmed by a central laboratory based on a second repeat blood sample drawn within 2 weeks of site notification of an inhibitor and all subjects who did not develop an inhibitor and had ≥100 EDs when the sample for the last valid inhibitor test was drawn.

13.4.2 Secondary Outcome Measures

13.4.2.1 Secondary Safety Outcome Measures

13.4.2.1.1 Binding antibodies to FVIII, PEG-FVIII and PEG

Histograms will be used to show number and proportion of subjects with/who

- Pre-existing binding antibodies
- Did not develop any binding antibodies
- Developed transient binding antibodies
- Developed persistent binding antibodies

The histograms will also be broken down by year of BAX 855 exposure (first year after first BAX 855 exposure, second year after first BAX 855 exposure, etc.).

13.4.2.1.2 AEs and SAEs

A summary table will contain the number and percentage of subjects reporting serious adverse events (SAEs), treatment-associated systemic AEs, moderate or severe systemic AEs, any systemic AEs, moderate or severe local AEs, and any local AEs.

13.4.2.1.3 Vital signs and clinical laboratory parameters

Clinically significant changes in vital signs and clinical laboratory parameters (hematology and clinical chemistry)

Shift tables will be used to assess the frequency of changes from clinically significant vital signs and clinical laboratory parameters (hematology and clinical chemistry) to not clinically significant changes or vice versa by year after first exposure to BAX 855.

13.4.2.2 Secondary Efficacy Outcome Measures

13.4.2.2.1 Annualized bleeding rate (ABR) for prophylactic and on-demand treatment

The ABR will be analyzed by point and interval estimates derived from a negative binomial model with treatment regimen (on-demand vs. prophylaxis) as a covariate and the duration of the observation period as an offset.

13.4.2.2.2 Number of BAX 855 infusions per bleeding episode and overall hemostatic efficacy rating at 24 h after initiation of treatment and at resolution of bleed

Frequency tables will be prepared for the number of BAX 855 infusions per bleeding episode and overall hemostatic efficacy rating at 24 h after initiation of treatment and at resolution of bleed broken down by treatment regimen and severity (mild, moderate or severe).

13.4.2.2.3 Weight-adjusted consumption of BAX 855 per month, per year and per event (prophylaxis, treatment of bleeding episode, surgery) and the number of infusions per month and per year

Descriptive statistics (mean, SD, median, quartiles and ranges) will be given for weight-adjusted consumption of BAX 855 per month, per year and per event (prophylaxis, treatment of bleeding episode, surgery) and the number of infusions per month and per year.

13.4.2.2.4 Assessment of intra-, post- and perioperative hemostatic efficacy in case of surgery

Descriptive statistics (mean, SD, median, quartiles and ranges) will be given for of intra-, post- and perioperative hemostatic efficacy parameters in case of surgery

13.4.2.2.5 Intra- and postoperative blood loss in case of surgery

Descriptive statistics (mean, SD, median, quartiles and ranges) will be given for intra- and postoperative blood loss in case of surgery.

13.4.2.3 Secondary Pharmacokinetic Outcome Measures

13.4.2.3.1 IR at baseline and over time

Descriptive statistics (mean, SD, median, quartiles and ranges) will be presented for IR at baseline, and each year after first exposure to BAX 855.

13.4.2.3.2 Half-life at baseline (optional)

Half-life at baseline will be listed per subject, if available.

13.4.2.4 Additional Outcome Measures for ITI

Primary:

The success rate of ITI therapy with BAX 855, success being defined as 1) a persistently negative inhibitor titer <0.6 BU, 2) FVIII IR ≥66% of initial baseline value following a wash-out period of 84-96 h, and 3) a FVIII half-life of ≥6 hours. If no baseline IR is available, an IR value indicative of an adequate clinical response following a wash-out period of 84-96 hours will be used for the definition of success. An adequate clinical response is defined as pharmacokinetic parameters that permit effective prophylactic treatment of the study subject, including maintenance of FVIII levels above 1%.

The number and proportion of success in ITI will be given.

Secondary:

- *The rate of partial success and failure of ITI with BAX 855*
  The number and proportion of success in ITI will be given.
- *ABR during ITI*
  The ABR during ITI will be estimated by a negative binomial model.
- *Weight-adjusted consumption of BAX 855 per month and per year for each ITI regimen employed*
  Descriptive statistics (mean, SD, median, quartiles and ranges) will be used for weight-adjusted consumption of BAX 855 per month and per year for each ITI regimen employed.
- *Catheter-related complications*
  The frequency per subject and per subject-year of catheter-related complications will be calculated.

- *Binding antibodies to FVIII, PEG-FVIII, and PEG*
  Histograms will be used to show the number and proportion of subjects with/who
  - Pre-existing binding antibodies
  - Did not develop any binding antibodies
  - Developed transient binding antibodies
  - Developed persistent binding antibodies

  The histograms will also be broken down by year of BAX 855 exposure (first year after start of ITI, second year after start of ITI, etc.).

The analysis of efficacy will be stratified by subjects who received BAX 855 as a single agent for ITI and subjects who used BAX 855 plus an immune modulatory agent, if applicable. Separate analyses of data from subjects dosed with the 2 dosing regimens of 50 IU/kg 3 x weekly and 100-200 IU/kg daily will be performed.

13.4.3 Exploratory Outcome Measures

[redacted]

13.5 Planned Interim Analysis of the Study

An interim analysis will be performed once 50 subjects have accumulated at least 50 EDs to BAX 855 or have developed a confirmed inhibitor to FVIII for regulatory purposes and will comprise the same analyses planned for the final data set. Results will be described in an interim clinical study report.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

14.1 Changes Due to COVID-19 Pandemic: Remote Source Document Verification (rSDV)

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source document verification (rSDV) or telephone contact may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used only where allowed by the local Health Authority and permitted by the IRB/IEC.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

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

15.1.1 Final Clinical Study Report

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

15.2 Training

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

15.3 Monitoring

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

15.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements.

The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

15.5 Non-Compliance with the Protocol

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

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

15.6 Laboratory and Reader Standardization

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

16. ETHICS

16.1 Subject Privacy

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

16.2 Ethics Committee and Regulatory Authorities

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

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

16.3 Informed Consent

Investigators will enroll patients who meet the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

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

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

16.4 Data Monitoring Committee

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

The sponsor will formally convene this panel for review of the study data at least once per year until completion of the study. Ad hoc convocations of the DMC will occur on an as-needed basis. If the inhibitor incidence is above 41% of the total study cohort (the 95% confidence interval upper limit of that observed in the ADVATE PUP study) after at least the first 10 subjects are enrolled, then the data will be presented to the DMC for review.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

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

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.8), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, 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, including source documentation for the change performed. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

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

17.3 Document and Data Retention

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

18. FINANCING AND INSURANCE

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

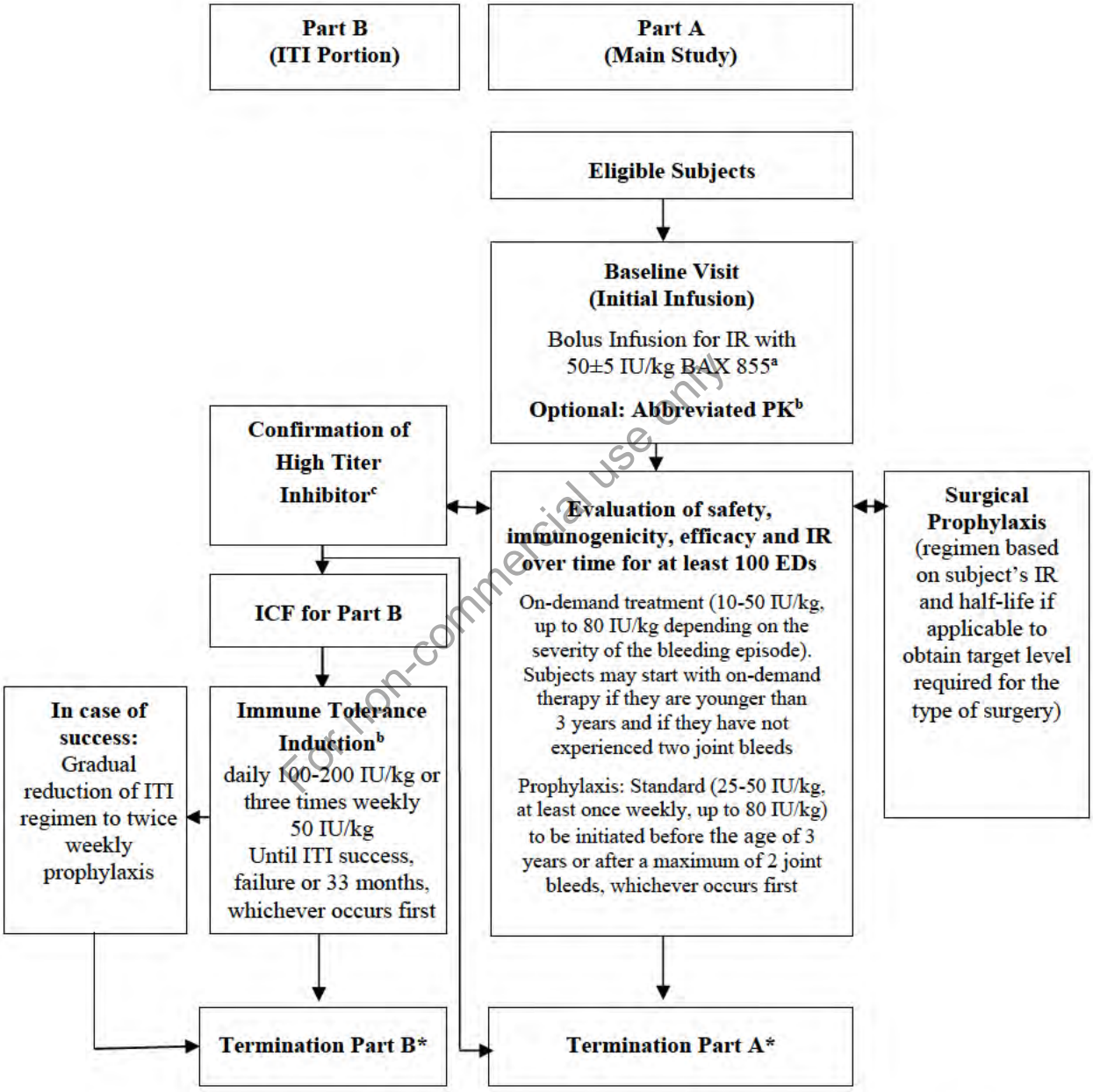
19. PUBLICATION POLICY

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

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 1. Study Design for Clinical Study 261203



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

20.2 Detailed Flow Diagram of Study Procedures

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

If at any time during Part A:

- a subject requires a surgical, dental or invasive procedure, the dosing procedures described in Section 8.7.3.5 and Section 22 should be followed.
- a subject develops a confirmed high titer inhibitor (>5 BU/mL) or a low titer inhibitor (≥0.6 but ≤5 BU/mL) with poorly controlled bleeding despite increased BAX 855 doses or requiring bypassing agents to treat bleeding , the subject can be entered in Part B of the study for ITI. The decision may be based on the results determined at the local laboratory, but must be confirmed by the central laboratory. In case the central laboratory does not confirm the presence of a positive FVIII inhibitor with a second repeat blood sample, ITI therapy including the use of bypassing agents will be discontinued and the treatment regimen as defined for Part A will be resumed.
- a subject experiences a severe hypersensitivity reaction, an additional blood sample has to be drawn to test for the presence of IgE antibodies against FVIII and PEG.
- there is a situation in which a prolonged treatment of a bleed results in a cumulative ED count that exceeds a specific ED-directed visit, the ED-directed visit should take place at the next non-bleeding infusion, where feasible. For example, a subject with 2 EDs who requires 5 EDs to treat a bleed would accumulate 7 EDs and miss study Visit 1 (5 ± 1 ED) at the scheduled time. Study Visit 1 should be completed at ED 8 and continue with study Visit 2 at the appropriate time (10 ± 1 EDs)
- there is a situation in which 2 or more ED-directed visits must be missed due to ongoing bleeding treatment, the most recent, omitted visit should be conducted at the first non-bleeding ED, where feasible. For example, a subject with 2 EDs who requires 10 EDs to treat a bleed would accumulate 12 EDs and miss study Visits 1 (5 ± 1 EDs) and 2 (10 ± 1 EDs) at the scheduled times. Study Visit 2 should be completed at ED 12 and continue with study Visit 3 at the appropriate time (15 ± 1 EDs)

20.2.1 Detailed Flow Diagram of Study Procedures for Part A

Part A: Screening Visit

Written informed consent and, if appropriate, written assent must be obtained from each participant/their parent/legal guardian before any study related procedures are performed. The subject must not be actively bleeding at the screening visit.

The Screening Visit procedures (which start with the first blood draw), including laboratory evaluations, are to be completed within 45 days prior to the first infusion of IP or repeated if more than 45 days have elapsed.

The following screening procedures will be performed:

- Assessment of inclusion/exclusion criteria.
- Clinical Assessments:
  - Medical history.
  - Hemophilia history, including:
    - Confirmation of diagnosis and severity.
    - Family history of hemophilia, including inhibitor development, if known.
    - FVIII gene mutation analysis and HLA genotype, if available.
    - The presence of any target joints will be documented.
    - [redacted]
  - Record any medications and non-drug therapies given in last 30 days, and any prior history of use of any PEGylated medication (eg, PEG-interferon), plasma, cryoprecipitate, any type of FVIII concentrate, or any kind of blood-transfusion such as PRBC, platelets or plasma at any time in the past, including treatment indication, date of last administration, and duration of treatment(s), if known.
  - Physical exam
  - Vital signs (body temperature [°C], respiratory rate [breaths/min], pulse rate [beats/min], and systolic and diastolic blood pressure [mmHg]). Blood pressure will be measured with subjects in a supine position. Measure height (cm) and weight (kg).
- Laboratory Assessments (may be staggered during screening period):
  - FVIII assays:
    - FVIII activity (one-stage clotting assay and chromogenic assay).
  - Immunogenicity tests:
    - Inhibitory antibodies to FVIII (Nijmegen modification of the Bethesda assay).
    - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]
  - Hematology, clinical chemistry
  - CD4 count

Subject diary:

- Hand out subject electronic diary and provide training to subject/their parent/legal guardian

Part A: Baseline Visit

If the subject has received an infusion of a FVIII product prior to baseline there must be a minimum wash-out period of at least 72 hours. The subject must not be actively bleeding. Eligibility to be confirmed by site and Medical Advisor prior to baseline visit.

Pre-infusion, the following assessments will be carried out:

- Physical examination
- Vital signs (within 15 minutes of start of infusion), including body weight
- FVIII assays (within 30 minutes of start of infusion)
- Immunogenicity tests (within 30 minutes of start of infusion):
    - Inhibitory antibodies to FVIII (Nijmegen assay)
    - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]

Infusion:

- Infusion of BAX 855 at dose of 50 ± 5 IU/kg. In case of on-demand therapy or low dose prophylactic treatment, a lower dose for IR determination may be considered but should not be lower than 25 IU/kg.
- For optional PK assessment, the dose for PK should be 50 ± 5 IU/kg BAX 855.

Post-infusion:

- Laboratory Assessments
    - FVIII recovery at 15-30 minutes after start of infusion
    - In those subjects who undergo the optional PK assessment an additional sample will be taken at 24-48 h post-infusion
- Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure) at 15-30 minutes after start of infusion

Other procedures:

- Dispense IP:
    - Provide sufficient BAX 855 until at least the next scheduled visit, or as appropriate, for prophylactic therapy or on-demand therapy (only if subject <3 years old and experienced <2 joint bleeds)
- Assessment of any bleeding episodes and target joint bleedings
- Review subject diary

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

- Adverse events
- Concomitant medications and non-drug therapies

(Part A: On-Demand Visit)
On demand visits occur every 3 months (± 2 weeks) after baseline until the Visit 1 criterion of 5 ± 1 EDs is met. If fewer than 3 months elapse between Baseline Visit and 5 ± 1 EDs, then this visit is not required. The following assessments will be carried out: • Physical examination • Vital signs, including body weight Other procedures: • Dispense IP: o Provide sufficient BAX 855 until at least the next scheduled visit, or as appropriate, for prophylactic therapy or on-demand therapy (only if subject <3 years old and experienced <2 joint bleeds) • Assessment of any bleeding episodes and target joint bleedings • Review subject diary Throughout the visit, the following assessments will be carried out: • Adverse events • Concomitant medications and non-drug therapies

Part A: Visit 1
5 ± 1 EDs

There must be a minimum wash-out period of at least 84 – 96 h after the last BAX 855 infusion and the subject must not be actively bleeding. Visit is to occur at next non-bleeding ED if EDs 4-6 are accounted for by BAX 855 infusions for bleeding treatment.

The following assessments will be carried out:

- Physical examination
- Immunogenicity tests:
  - Inhibitory antibodies to FVIII (Nijmegen assay)
  - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]
- FVIII assays (within 30 minutes of start of infusion) (optional)

Infusion (optional):

- Infusion of BAX 855 at dose of 50 ± 5 IU/kg. In case of low dose prophylactic treatment, a lower dose for IR determination may be considered, but should not be lower than 25 IU/kg.
- For optional PK assessment, the dose for PK should be 50 ± 5 IU/kg BAX 855.

Post-infusion (optional)

- Laboratory Assessments
  - FVIII recovery at 15-30 minutes after start of infusion

Other procedures:

- Assessment of any bleeding episodes and target joint bleedings
- Review subject diary
- Dispense IP (provide sufficient BAX 855 until at least the next scheduled visit, or as appropriate)

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

- Adverse events
- Concomitant medications and non-drug therapies

Part A: Visit 2
10 ± 1 EDs

There must be a minimum wash-out period of at least 84 – 96 h after the last BAX 855 infusion and the subject must not be actively bleeding. Visit is to occur at next non-bleeding ED if EDs 9-11 are accounted for by BAX 855 infusions for bleeding treatment.

Pre-infusion, the following assessments will be carried out:

- FVIII assays (within 30 minutes of start of infusion)
- Vital signs (within 15 minutes of start of infusion), including body weight
- Immunogenicity tests (within 30 minutes of start of infusion):
  - Inhibitory antibodies to FVIII (Nijmegen assay)
  - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]

Infusion:

- Infusion of dose of BAX 855 at dose of 50 ± 5 IU/kg. In case of low dose prophylactic treatment, a lower dose for IR determination may be considered, but should not be lower than 25 IU/kg.
- For optional PK assessment, the dose for PK should be 50 ± 5 IU/kg BAX 855.

Post-infusion:

- Laboratory Assessments
  - FVIII recovery at 15-30 minutes after start of infusion
- Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure) at 15-30 minutes after start of infusion

Other procedures:

- Assessment of any bleeding episodes and target joint bleedings
- Review subject diary
- Dispense IP (provide sufficient BAX 855 until at least the next scheduled visit, or as appropriate)

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

- Adverse events
- Concomitant medications and non-drug therapies

Part A: Visit 3
15 ± 1 EDs

There must be a minimum wash-out period of at least 84 – 96 h after the last BAX 855 infusion and the subject must not be actively bleeding. Visit is to occur at next non-bleeding ED if EDs 14-16 are accounted for by BAX 855 infusions for bleeding treatment.

The following assessments will be carried out:

- Physical examination
- Immunogenicity tests:
  - Inhibitory antibodies to FVIII (Nijmegen assay)
  - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]
- FVIII assays (within 30 minutes of start of infusion) (optional)

Infusion (optional):

- Infusion of BAX 855 at dose of 50 ± 5 IU/kg. In case of low dose prophylactic treatment, a lower dose for IR determination may be considered, but should not be lower than 25 IU/kg.

Post-infusion (optional)

- Laboratory Assessments
  - FVIII recovery at 15-30 minutes after start of infusion

Other procedures:

- Assessment of any bleeding episodes and target joint bleedings
- Review subject diary
- Dispense IP (provide sufficient BAX 855 until at least the next scheduled visit, or as appropriate)

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

- Adverse events
- Concomitant medications and non-drug therapies

Part A: Visit 4
20 ± 2 EDs

There must be a minimum wash-out period of at least 84 – 96 h after the last BAX 855 infusion and the subject must not be actively bleeding. Visit is to occur at next non-bleeding ED if EDs 18-22 are accounted for by BAX 855 infusions for bleeding treatment.

Pre-infusion, the following assessments will be carried out:

- FVIII assays (within 30 minutes of start of infusion)
- Vital signs (within 15 minutes of start of infusion), including body weight. Height if 6 months from baseline.
- Immunogenicity tests (within 30 minutes of start of infusion):
  - Inhibitory antibodies to FVIII (Nijmegen assay)
  - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]

Infusion:

- Infusion of BAX 855 at dose of 50 ± 5 IU/kg. In case of low dose prophylactic treatment, a lower dose for IR determination may be considered but should not be lower than 25 IU/kg.

Post-infusion:

- Laboratory Assessments
  - FVIII recovery at 15-30 minutes after start of infusion
- Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure) at 15-30 minutes after start of infusion

Other procedures:

- Assessment of any bleeding episodes and target joint bleedings
- Review subject diary
- Dispense IP (provide sufficient BAX 855 until at least the next scheduled visit, or as appropriate)

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

- Adverse events
- Concomitant medications and non-drug therapies

Part A: Visit 5
30 ± 3 EDs

There must be a minimum wash-out period of at least 84 – 96 h after the last BAX 855 infusion and the subject must not be actively bleeding.

This visit should take place *before* 30 EDs if **3 months** have elapsed since Visit 4.

Pre-infusion, the following assessments will be carried out:

- Physical examination
- Vital signs (within 15 minutes of start of infusion), including body weight
- Laboratory tests: hematology and clinical chemistry
- Immunogenicity tests (within 30 minutes of start of infusion):
    - Inhibitory antibodies to FVIII (Nijmegen assay)
    - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]
- FVIII assays (within 30 minutes of start of infusion) (optional)

Infusion (optional):

- Infusion of BAX 855 at dose of 50 ± 5 IU/kg. In case of low dose prophylactic treatment, a lower dose for IR determination may be considered but should not be lower than 25 IU/kg.

Post-infusion (optional):

- Laboratory Assessments
    - FVIII recovery at 15-30 minutes after start of infusion

Other procedures:

- Dispense IP (provide sufficient BAX 855 until at least the next scheduled visit, or as appropriate)
- Assessment of any bleeding episodes and target joint bleedings
- Review subject diary

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

- Adverse events
- Concomitant medications and non-drug therapies

Part A: Visit 6
40 ± 3 EDs

There must be a minimum wash-out period of at least 84 – 96 h after the last BAX 855 infusion and the subject must not be actively bleeding.

This visit should take place *before* 40 EDs if **3 months** have elapsed since Visit 5.

Pre-infusion, the following assessments will be carried out:

- Physical examination (optional)
- Vital signs (within 15 minutes of start of infusion), including body weight
- FVIII assays (within 30 minutes of start of infusion)
- Immunogenicity tests (within 30 minutes of start of infusion):
    - Inhibitory antibodies to FVIII (Nijmegen assay)
    - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]

Infusion:

- Infusion of BAX 855 at dose of 50 ± 5 IU/kg. In case of low dose prophylactic treatment, a lower dose for IR determination may be considered but should not be lower than 25 IU/kg.

Post-infusion:

- Laboratory Assessments
    - FVIII recovery at 15-30 minutes after start of infusion
- Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure) at 15-30 minutes after start of infusion

Other procedures:

- Assessment of any bleeding episodes and target joint bleedings
- Review subject diary
- Dispense IP (provide sufficient BAX 855 until at least the next scheduled visit, or as appropriate)

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

- Adverse events
- Concomitant medications and non-drug therapies

Part A: Visit 7
50 – 55 EDs

There must be a minimum wash-out period of at least 84 – 96 h after the last BAX 855 infusion and the subject must not be actively bleeding.

This visit should take place *before* 50 EDs if **3 months** have elapsed since Visit 6.

Pre-infusion, the following assessments will be carried out:

- Physical examination
- Vital signs (within 15 minutes of start of infusion), including body weight, and height if 6 months have elapsed since previous measurement
- Laboratory tests: hematology (if 3 months or 30 EDs have elapsed since the previous sample) and clinical chemistry
- NB: CD4 count must be reassessed after every 12 months in the study. Check the date of the subject's baseline visit and take sample as required.
- FVIII assays (within 30 minutes of start of infusion)
- Immunogenicity tests (within 30 minutes of start of infusion):
    - Inhibitory antibodies to FVIII (Nijmegen assay)
    - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]

Infusion:

- Infusion of BAX 855 at dose of 50 ± 5 IU/kg. In case of low dose prophylactic treatment, a lower dose for IR determination may be considered but should not be lower than 25 IU/kg.

Post-infusion:

- Laboratory Assessments
    - FVIII recovery at 15-30 minutes after start of infusion
- Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure) at 15-30 minutes after start of infusion

Other procedures:

- Dispense IP (provide sufficient BAX 855 until at least the next scheduled visit, or as appropriate)
- Assessment of any bleeding episodes and target joint bleedings
- Review subject diary

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

- Adverse events
- Concomitant medications and non-drug therapies

Part A: Visit 8*
75 ± 5 EDs

There must be a minimum wash-out period of at least 84 – 96 h after the last BAX 855 infusion and the subject must not be actively bleeding.

Pre-infusion, the following assessments will be carried out:

- Physical examination
- Vital signs (within 15 minutes of start of infusion), including body weight, and height if 6 months have elapsed since previous measurement
- Laboratory tests: hematology (if 3 months or 30 EDs have elapsed since the previous sample)
- NB: CD4 count must be reassessed after every 12 months in the study. Check the date of the subject's baseline visit and take sample as required.
- FVIII assays (within 30 minutes of start of infusion)
- Immunogenicity tests (within 30 minutes of start of infusion):
    - Inhibitory antibodies to FVIII (Nijmegen assay)
    - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]

Infusion:

- Infusion of BAX 855 at dose of 50 ± 5 IU/kg.

Post-infusion:

- Laboratory Assessments
    - FVIII recovery at 15-30 minutes after start of infusion
- Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure) at 15-30 minutes after start of infusion

Other procedures:

- Dispense IP (provide sufficient BAX 855 until at least the next scheduled visit, or as appropriate)
- Assessment of any bleeding episodes and target joint bleedings
- Review subject diary

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

- Adverse events
- Concomitant medications and non-drug therapies

* For the unscheduled visits to be performed every 3 months, subjects on optional extended prophylaxis with BAX 855 will follow the procedures for Visit 8.

Part A: Completion/Termination Visit
100 – 110 EDs

There must be a minimum wash-out period of at least 84 – 96 h after the last BAX 855 infusion and the subject must not be actively bleeding.

Pre-infusion, the following assessments will be carried out:

- Physical examination
- Vital signs (within 15 minutes of start of infusion), including body weight. Height if 6 months since last measurement.
- Laboratory tests: hematology and clinical chemistry
- NB: CD4 count must be reassessed every 12 months in the study. Check the date of the subject's baseline visit and take sample as required.
- FVIII assays (within 30 minutes of start of infusion)
- Immunogenicity tests (within 30 minutes of start of infusion):
    - Inhibitory antibodies to FVIII (Nijmegen assay)
    - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]

Infusion:

- Infusion of BAX 855 at dose of 50 ± 5 IU/kg

Post-infusion:

- Laboratory Assessments
    - FVIII recovery at 15-30 minutes after start of infusion
- Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure) at 15-30 minutes after start of infusion

Other procedures:

- Assessment of any bleeding episodes and target joint bleedings
- Hand in subject diary and review

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

- Adverse events
- Concomitant medications and non-drug therapies

20.2.2 Detailed Flow Diagram of Study Procedures for Part B

If during Part B:

- a subject has a severe hypersensitivity reaction, an additional blood sample has to be drawn to test for the presence of IgE antibodies against FVIII and PEG.
- a subject must undergo a surgical intervention, there are no protocol-defined treatment regimens, but the use of any bypassing agents should be recorded as concomitant medications.
- a subject does not initiate ITI within the first month, FVIII and immunogenicity labs should be assessed monthly until ITI initiation
- after the first 3 months of treatment, a subject does **not** have a 20% reduction in inhibitor titer relative to the peak inhibitor titer over any six-month period (in the absence of infection which in the opinion of the investigator could be expected to result in elevated inhibitor titers), ITI therapy will be considered a failure and a Completion/Termination Visit should be performed at a time deemed feasible by the investigator and sponsor.

In order to ensure timely availability of FVIII inhibitor results enabling the clinical management of the subject, results of the local laboratory may be used. However, if ITI has been initiated based on results of the local laboratory and a FVIII inhibitor is not confirmed by the central laboratory by the second repeat blood sample drawn within 2 weeks of study site notification of an inhibitor, the subject will resume his original treatment regimen with BAX 855 as defined in Part A and discontinue ITI therapy. The subject will be transitioned back to Part A.

Part B: Screening Visit

Written informed consent and, if appropriate, written assent must be obtained from each participant and their parent/legal guardian before any study related procedures are performed. The following screening procedures will be performed:

- Assessment of inclusion/exclusion criteria for Part B.
- Clinical Assessments:
  - Physical exam
  - Vital signs (body temperature [°C], respiratory rate [breaths/min], pulse rate [beats/min], and systolic and diastolic blood pressure [mmHg]). Blood pressure will be measured with subjects in a supine position. Measure height (cm) and weight (kg).
- Laboratory Assessments:
  - Hematology, clinical chemistry
  - Immunogenicity tests:
    - Inhibitory antibodies to FVIII (Nijmegen modification of the Bethesda assay).
    - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]

Subject diary:

- Hand out subject electronic diary and provide training to subject/subject's parent/legal guardian

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

- Concomitant medications and non-drug therapies
- Adverse events

Part B: First ITI infusion

The first ITI infusion can be given on the same day as the Screening Visit, if desired, provided that all eligibility criteria have been confirmed.

Pre-infusion, the following assessments will be carried out:

- Immunogenicity tests (within 30 minutes of start of infusion):
  - Inhibitory antibodies to FVIII (Nijmegen assay)
  - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]

Infusion:

- Infusion of BAX 855 at a dose of 50 ± 5 IU/kg or 100-200 ± 10 IU/kg

Other procedures:

- Dispense IP: provide sufficient BAX 855 for 1 month ± 1 week for ITI therapy.
- Assessment of any bleeding episodes and target joint bleedings
- Review subject diary

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

- Adverse events
- Concomitant medications and non-drug therapies

Part B: Visit 1
Week 2 ± 2 days

There must be a minimum wash-out period of preferably 48 h after the last BAX 855 infusion, or the longest time interval possible without undue interruption to the ITI therapy schedule, and the subject must not be actively bleeding.

Pre-infusion, the following assessments will be carried out:

- Physical examination
- Vital signs (within 15 minutes of start of infusion), including body weight
- Immunogenicity tests (within 30 minutes of start of infusion):
  - Inhibitory antibodies to FVIII (Nijmegen assay)
  - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]

Infusion:

- Infusion of BAX 855 at a dose of 50 ± 5 IU/kg or 100-200 ± 10 IU/kg

Post-infusion:

- Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure) at 15-30 minutes after start of infusion

Other procedures:

- Assessment of any bleeding episodes and target joint bleedings
- Review subject diary

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

- Adverse events
- Concomitant medications and non-drug therapies

Part B: Visit 2
Week 4 ± 2 days

There must be a minimum wash-out period of preferably 48 h after the last BAX 855 infusion, or the longest time interval possible without undue interruption to the ITI therapy schedule, and the subject must not be actively bleeding.

Pre-infusion, the following assessments will be carried out:

- Immunogenicity tests (within 30 minutes of start of infusion):
  - Inhibitory antibodies to FVIII (Nijmegen assay)
  - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]

Infusion:

- Infusion of BAX 855 at a dose of 50 ± 5 IU/kg or 100-200 ± 10 IU/kg

Other procedures:

- Assessment of any bleeding episodes and target joint bleedings
- Review subject diary

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

- Adverse events
- Concomitant medications and non-drug therapies

Part B: Follow-up Visits
Monthly intervals ± 1 week

There must be a minimum wash-out period of preferably 48 h after the last BAX 855 infusion, or the longest time interval possible without undue interruption to the ITI therapy schedule, and the subject must not be actively bleeding.

At the follow-up visits in Part B, IR is assessed once a subject has 2 negative inhibitor titers within a two-month period (minimum 3 weeks apart) and will be repeated until IR is ≥66% of the initial baseline IR value in Part A. The IR should be performed with 50 ± 5 IU/kg, however, in order to avoid undue interruption of the therapy schedule, the same dose may be used for IR determination.

If IR is ≥66% of the initial baseline value:

- ITI should be continued and IR with BAX 855 repeated within 1 month after a wash-out period of at least **84-96 h** or the longest time interval possible without undue interruption to the ITI therapy schedule.
- If IR is again ≥66% of initial value, ITI therapy will be continued and a FVIII half-life determination performed within 2 months after a wash-out period of at least 84-96 h.
- When IR is ≥66% of initial value and FVIII half-life ≥6 hours, **ITI will be considered successful**.

If IR is <66% of the initial baseline value:

- ITI therapy should be continued and BAX 855 IR repeated monthly after the longest time interval possible (preferably 48 hours), however, without undue interruption to the ITI therapy schedule until BAX 855 IR is ≥66% of the initial value.
- ITI should be continued and IR with BAX 855 repeated within 2 months (minimum 3 weeks apart) after a wash-out period of at least 84-96 h or the longest time interval possible without undue interruption to the ITI therapy schedule.
- If IR is again ≥66% of initial value, the same procedures should be followed as described under "If IR is >66% of the initial baseline value".
- If IR remains <66% of the initial value, it should be repeated until a maximum of 33 months of ITI has been provided and a Completion/Termination Visit will be performed at a time deemed feasible by the investigator and sponsor.

In case no initial baseline IR of Part A is available, the same procedures as described above should be performed. The baseline IR value of 66% is replaced by an IR indicative of an adequate clinical response which is defined as pharmacokinetic parameters that permit effective prophylactic treatment of the study subject, including maintenance of FVIII levels above 1%.

Pre-infusion, the following assessments will be carried out:

- Physical examination
- Vital signs (within 15 minutes of start of infusion), including body weight, and height if 6 months have elapsed since previous measurement
- If 2 negative inhibitor titers (see note above): FVIII assays (within 30 minutes of start of infusion)
- Immunogenicity tests (within 30 minutes of start of infusion):

Part B: Follow-up Visits
Monthly intervals ± 1 week

- Inhibitory antibodies to FVIII (Nijmegen assay)
- Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]

- CD4 (to be tested every year)
- Hematology and clinical chemistry (to be tested every 3 months)

Infusion:

- Infusion of BAX 855 at dose of 50 ± 5 IU/kg or 100-200 IU/kg ± 10 IU/kg

Post-infusion:

- FVIII recovery at 15-30 minutes after start of infusion (if IR is being assessed)
- For determination of FVIII half-life, if applicable, post-infusion blood draw at 24-48 hours
- Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure) at 15-30 minutes after start of infusion

Other procedures:

- Dispense IP: provide sufficient BAX 855 for 1 month ± 1 week for ITI therapy.
- Assessment of any bleeding episodes and target joint bleedings
- Review subject diary

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

- Adverse events
- Concomitant medications and non-drug therapies

Part B: In case of Success
Reducing ITI Dose to Twice Weekly Prophylaxis

In case of success, high-dose ITI regimen will be reduced to twice weekly prophylaxis as follows:

- 100 ± 5 IU/kg/day for the first 4 weeks, in case subject's initial ITI therapy consisted of 200 IU/kg/day; then
- 50 ± 5 IU/kg/day for a further 4 weeks; then
- 50 ± 5 IU/kg every second day for a further 4 weeks; then
- 50 ± 5 IU/kg administered twice a week, adjusted as needed to maintain a FVIII trough level of 1%, for a further 3 months.

In case of low dose ITI with 50 IU/kg 3 x weekly, subjects will be transitioned to twice weekly 50 ± 5 IU/kg prophylaxis , adjusted as needed to maintain a FVIII trough level of 1%, for 3 months.

Prior to each dose adjustment, the following procedures will be performed. If FVIII inhibitor recurs and/or FVIII IR is <66% of the initial baseline value, the subject should be transitioned back to the next higher dose (see Figure 2 for a detailed description of procedures and Section 12.7.2.1).

Pre-infusion, the following assessments will be carried out:

- Physical examination
- Vital signs (within 15 minutes before start of infusion), including body weight, and height if 6 months have elapsed since previous measurement
- Immunogenicity tests (within 30 minutes before start of infusion):
  - Inhibitory antibodies to FVIII (Nijmegen assay)
  - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII. [redacted]
- Hematology and clinical chemistry (to be tested every 3 months)

Infusion:

- Infusion of BAX 855 at dose of 50 ± 5 IU/kg, however, in order to avoid undue interruption of ITI therapy, the same ITI dose may be used for IR determination.

Post-infusion:

- FVIII recovery at 15-30 minutes after start of infusion (if IR is being assessed)
- For determination of FVIII half-life, if applicable, post-infusion blood draw at 24 – 48 h
- Vital signs (body temperature, respiratory rate, pulse rate, and supine systolic and diastolic blood pressure) at 15-30 minutes after start of infusion

Other procedures:

- Dispense IP: provide sufficient BAX 855 for 1 month ± 1 week for ITI therapy.
- Assessment of any bleeding episodes and target joint bleedings
- Review subject diary

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

- Adverse events
- Concomitant medications and non-drug therapies

Part B: Completion/Termination Visit
Treatment Success, Failure or at 33 Months (whichever occurs first)

There must be a minimum wash-out period of at least 84-96 h after the last BAX 855 treatment in case of treatment success and dose reduction to twice weekly infusions of BAX 855. The subject must not be actively bleeding during the Completion/Termination Visit.

The following assessments will be carried out:

- Physical examination
- Vital signs (within 15 minutes of start of infusion), including body weight, and height if 6 months have elapsed since the last measurement
- Laboratory tests: hematology and clinical chemistry
- Immunogenicity tests (within 30 minutes of start of infusion):
    - Inhibitory antibodies to FVIII (Nijmegen assay)
    - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEG-FVIII, and PEG. [redacted]

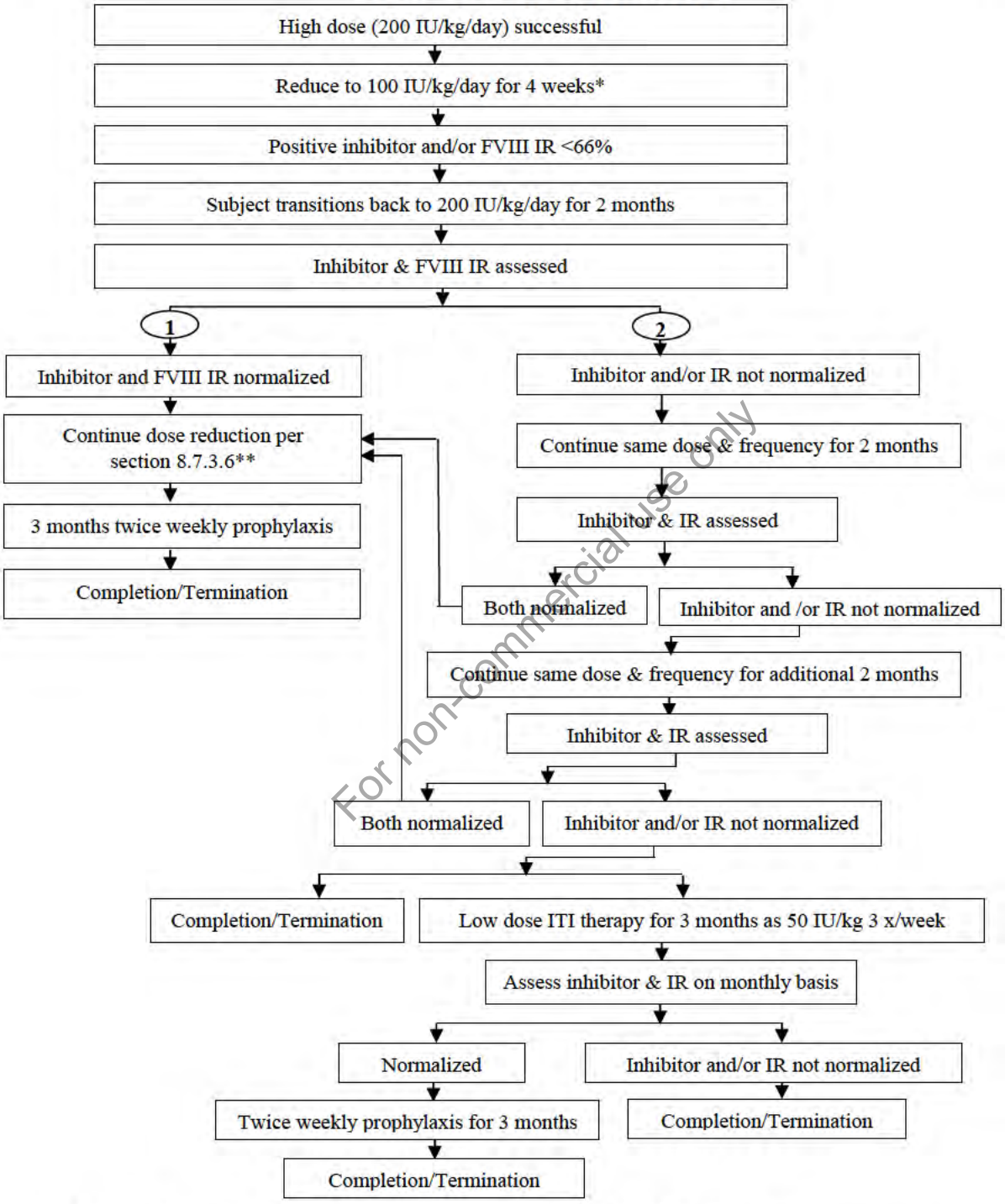
Other procedures:

- Assessment of any bleeding episodes and target joint bleedings
- Hand in subject diary and review

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

- Adverse events
- Concomitant medications and non-drug therapies

Figure 2
Procedure during the transition period in case of a recurrence of positive inhibitor and/or an IR <66% after successful ITI



* In case ITI therapy consisted of 100 IU/kg/day, the next lower dose will be 50 IU/kg/day.
** In case a positive inhibitor and/or a FVIII IR <66% occur during one or more of the subsequent dose reduction steps, the same procedure as described in (2) will be followed.

20.3 Schedules for Part A (Main Study)

20.3.1 Schedule of Study Procedures and Assessments for Part A (Main Study)

Table 6
Schedule of Study Procedures and Assessments for Part A (Main Study)*

Procedures/ Assessments	ICF[a] Screening Visit	Baseline Visit	Study Visits									Completion/ Termination Visit[d] 100-110 EDs
			(On-demand interval visit)[b]	Visit 1 ED 5 ± 1	Visit 2 ED 10 ± 1	Visit 3 ED 15 ± 1	Visit 4 ED 20 ± 2	Visit 5 ED 30 ± 3[c]	Visit 6 ED 40 ± 3[c]	Visit 7 ED 50 – 55[c]	Visit 8 ED 75 ± 5	
Informed Consent	X											
Eligibility Criteria	X	X										
Hand-Out of Subject Diary	X											
Medical History	X											
Hemophilia History	X											
Concomitant Medications[e]	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug Therapies[e]	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam[f]	X	X	X	X		X		X	(X)	X	X	X
Vital Signs[g,h]	X	X	X	(X)	X	(X)	X	(X)	X	X	X	X
Adverse Events[e]		X	X	X	X	X	X	X	X	X	X	X
Bleeding Episodes and their Treatment[e]		X	X	X	X	X	X	X	X	X	X	X
Assessment for Joint Bleeding / Adjustment of Treatment, if applicable[i]		X	X	X	X	X	X	X	X	X	X	X
Review of Subject Diary		X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[j]	X	X		X	X	X	X	X	X	X	X	X
IP Treatment/IR Determination[k]		X		(X)	X	(X)	X	(X)	X	X	X	X
IP Dispense[l]		X	X	X	X	X	X	X	X	X	X	

Table 6
Schedule of Study Procedures and Assessments for Part A (Main Study)*

Procedures/ Assessments	ICF[a] Screening Visit	Baseline Visit	Study Visits								Completion/ Termination Visit[d]
			(On-demand interval visit)[b]	Visit 1 ED 5 ± 1	Visit 2 ED 10 ± 1	Visit 3 ED 15 ± 1	Visit 4 ED 20 ± 2	Visit 5 ED 30 ± 3[c]	Visit 6 ED 40 ± 3[c]	Visit 7 ED 50 – 55[c]	Visit 8 ED 75 ± 5	100-110 EDs

a. Occurs at enrollment (prior to any study-specific procedures). The Screening Visit procedures, including laboratory evaluations, are to be completed within 45 days prior to the first infusion of investigational product (IP) or repeated if more than 45 days have elapsed, after discussion with the Medical Advisor. The screening period starts with the first blood sample drawn.

b. On demand visits occur every 3 months (± 2 weeks) after baseline until the Visit 1 criterion of 5 ± 1 exposure days (EDs) is met. If fewer than 3 months elapse between Baseline Visit and 5 ± 1 EDs, then this visit is not required.

c. These visits should take place at the EDs shown or after 3 months since the previous visit, whichever comes first.

d. Includes cases of withdrawal, discontinuation, or optional extended access. For duration of optional extended access to IP refer to Section 8.3.2.

e. Adverse events, concomitant medications, non-drug therapies, and bleeding episodes and their treatment are discussed at these time points but will be continuously monitored in the interim.

f. In the event of surgery, a pre-operative physical exam should be recorded.

g. Includes height and weight at screening and weight at the pre-infusion assessments. Height will be measured every 6 months at the closest scheduled visit.

h. Pulse, respiration, supine blood pressure, and temperature to be assessed within 15 minutes prior to start of infusion and 15-30 minutes following infusion. In the event of surgery, pre-operative, post-operative Day 1, and day of discharge vital signs are recorded.

i. A target joint is defined as one in which there have been ≥3 bleeds during the past six-month study period.

j. For laboratory assessments, See Table 7. At all assessments, subjects must not be actively bleeding and whenever possible there should be a wash-out period of 84-96 hours, before the next scheduled BAX 855 infusion. In addition to the assessments shown, clinical laboratory assessment should be performed whenever clinically indicated.

k. BAX 855 is administered at the study site at baseline and every study visit other than study Visits 1 (5 ± 1 EDs), 3 (15 ± 1 EDs) and 5 (30 ± 3 EDs) for the determination of factor VIII (FVIII) incremental recovery (IR) and abbreviated pharmacokinetics (PK) at baseline, Visit 1, or Visit 2, if performed (optional). If the subject has received an infusion of a FVIII product prior to baseline there must be a minimum wash-out of at least 72 hours, and post-baseline there must be a minimum wash-out of at least 84-96 h after the last BAX 855 infusion. Whenever possible, the timing of the BAX 855 infusion at the study site should be in accordance with the subject's prophylactic treatment regimen, if applicable. For IR determination, a dose of 50 ± 5 IU/kg BAX 855 should be infused. In case of on-demand therapy or low dose prophylactic treatment, a lower dose for IR determination may be considered but should not be lower than 25 IU/kg BAX 855. Also, at baseline, Visit 1, or Visit 2 an optional half-life based on an abbreviated PK can be performed following a dose of 50 ± 5 IU/kg BAX 855. For this purpose, an additional blood sample should be drawn 24-48 hours post-infusion.

l. The IP should be dispensed to provide sufficient treatment until at least the next scheduled visit, or as appropriate.

(X) means the test is optional

* For the unscheduled visits to be performed every 3 months, subjects on optional extended access to BAX 855 will follow the procedures for Visit 8, including determination of IR.

20.3.2 Clinical Laboratory Assessments in Part A (Main Study)

Table 7
Clinical Laboratory Assessments in Part A (Main Study)[a,*]

Procedures/ Assessments	ICF Screening Visit	Baseline Visit	(On-demand interval visit)	Study Visits								
				Visit 1 ED 5 ± 1	Visit 2 ED 10 ± 1	Visit 3 ED 15 ± 1	Visit 4 ED 20 ± 2	Visit 5 ED 30 ± 3[b]	Visit 6 ED 40 ± 3[b]	Visit 7 ED 50 - 55[b]	Visit 8 ED 75 ± 5	Completion/ Termination Visit[c] 100 -110 EDs
Hematology[d]	X							X		X		X
Clinical Chemistry[e]	X							X		X		X
CD4 Count[f]	X						X[f]					
Genetics and HLA-genotype[g]	X											
FVIII Assays[h]	X[i]	X[j]		(X)[j]	X[j]	(X)	X	(X)	X	X	X	X
Immunogenicity[k]	X	X		X	X	X	X	X	X	X	X	X

[redacted]

a. In order to minimize the amount of blood to be drawn at a specific study visit, the required tests can be performed over a couple of days, however, for the determination of immunogenicity and incremental recovery (IR), the respective wash-out periods have to be considered.
b. These visits should take place at the exposure days (EDs) shown or after 3 months since the previous visit, whichever comes first.
c. Includes cases of withdrawal, discontinuation, or optional extended access. For duration of optional extended access to investigational product (IP) refer to Section 8.3.2.
d. Post screening hematology will be assessed every 3 months or 30 EDs, whichever occurs first. Hematology assessments include: hemoglobin, hematocrit, red blood cell count, and white blood cell count with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and platelet count. In the event of surgery, local hematology results, if any, should be recorded.
e. 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. In the event of surgery, local chemistry results, if any, should be recorded.
f. CD4 count is analyzed to determine subject's eligibility, thereafter every year.
g. If results of factor VIII (FVIII) gene mutation analysis and human leukocyte antigen (HLA) genotype are already available at the study site, they will be provided to the sponsor and an additional analysis will not be required.
h. Factor VIII assays include: FVIII one-stage clotting activity and FVIII chromogenic activity. If the subject has received an infusion of a FVIII product prior to baseline there must be a minimum wash-out of at least 72 hours, and post-baseline there must be a minimum wash-out of at least 84-96 h after the last BAX 855 infusion. For assessment of recovery: Blood samples for assessment of incremental recovery will be taken within 30 ± 5 minutes before and 15-30

Table 7
Clinical Laboratory Assessments in Part A (Main Study)[a,*]

Procedures/ Assessments	ICF Screening Visit	Baseline Visit	(On-demand interval visit)	Study Visits: Visit 1 ED 5 ± 1	Visit 2 ED 10 ± 1	Visit 3 ED 15 ± 1	Visit 4 ED 20 ± 2	Visit 5 ED 30 ± 3[b]	Visit 6 ED 40 ± 3[b]	Visit 7 ED 50 - 55[b]	Visit 8 ED 75 ± 5	Completion/ Termination Visit[c] 100 -110 EDs

minutes after IP infusion of 50 ± 5 IU/kg. In case of on-demand therapy or low dose prophylaxis treatment, a lower dose for IR determination may be considered, but should not be lower than 25 IU/kg. IR determination at visits 1 (5 ± 1 EDs), 3 (15 ± 1 EDs) and 5 (30 ± 3 EDs) are optional.

i. IR not at screening.

j. At baseline an optional abbreviated FVIII half-life may be performed. If the subject has received an infusion of a FVIII product prior to baseline there must be a minimum wash-out of at least 72 hours (for Visit 1 and 2, a minimum washout of at least 84-96 hours would be required). A blood sample will be drawn within 30 ± 5 minutes before, 15-30 minutes and 24-48 hours after IP infusion of 50 ± 5 IU/kg. If no abbreviated pharmacokinetics (PK) is performed, at least a 15-30 minute post-infusion blood draw for the determination of the initial FVIII recovery at baseline will be taken.

k. Immunogenicity assessments include: inhibitory antibodies to FVIII, binding antibodies to FVIII, BAX 855 and polyethylene glycol (PEG). Both IgG and IgM binding antibodies will be measured. [redacted]. If the subject has received an infusion of a FVIII product prior to baseline, there must be a minimum wash-out of at least 72 hours, and post-baseline there must be a minimum wash-out of at least 84-96 hours after the last BAX 855 infusion. Binding antibodies will be tested using plasma from citrated whole blood. In case of a severe hypersensitivity reaction an additional blood sample has to be drawn to test for the presence of IgE antibodies against FVIII and PEG-FVIII. To ensure the clinical management of the subject, clinical decisions to start bypassing agents in addition to BAX 855 may be based on the results of the local laboratory, however, back-up samples must be drawn to have the FVIII inhibitors determined at the central laboratory. If FVIII inhibitors are not confirmed at the central laboratory by a second repeat blood sample, no further bypassing agents may be administered. In case of a positive inhibitor ≥0.6 Bethesda Units (BU), a second repeat blood sample the central lab needs to be drawn within 2 weeks of study site notification of an inhibitor.

[redacted]

(X) means the test is optional

* For the unscheduled visits to be performed every 3 months, subjects on optional extended access to BAX 855 will follow the procedures for Visit 8.

20.4 Schedules for Part B (ITI Portion)

20.4.1 Schedule of Study Procedures and Assessments for Part B (ITI Portion)

Table 8
Schedule of Study Procedures and Assessments for Part B (ITI Portion)*

Procedures/ Assessments	ICF[a] Screening Visit	First ITI Infusion[b]	Study Visits			Completion/ Termination Visit[c] Success[l], Failure, or 33 Months, Whichever Occurs First
			Visit 1 Wk 2 ± 2 days	Visit 2 Wk 4 ± 2 days	FU Visits Monthly ± 1 week	
Informed Consent	X					
Eligibility Criteria	X					
Hand-Out of Subject Diary	X	X				
Concomitant Medications[d]	X	X	X	X	X	X
Non-drug Therapies[d]	X	X	X	X	X	X
Physical Exam	X	X	X		X	X
Vital Signs[e,f]	X	X	X		X	X
Adverse Events[d]		X	X	X	X	X
Bleeding Episodes and their Treatment[d,g]		X	X	X	X	X
Assessment for Joint Bleeding /Adjustment of Treatment, if applicable[h]		X	X	X	X	X
Review of Subject Diary		X	X	X	X	X
Laboratory Assessments[i]	X	X	X	X	X	X
IP Treatment/IR /Half-life Determination[j]		X	X	X	X	X
IP Dispense[k]		X	(X)	(X)	X	

a. Occurs at enrollment (prior to any study-specific procedures in Part B).
b. Screening and first immune tolerance induction (ITI) infusion can coincide depending when ITI is started. No incremental recovery (IR) is performed at first ITI infusion. ITI can be initiated based on a second repeat blood sample within 2 weeks of study site notification of inhibitor result determined at the local laboratory, however, if factor VIII (FVIII) inhibitor is not confirmed at the central laboratory, ITI therapy has to be discontinued and previous treatment regimen resumed. Subject will be transitioned back to Part A.
c. Includes cases of withdrawal or discontinuation.

Table 8
Schedule of Study Procedures and Assessments for Part B (ITI Portion)*

Procedures/ Assessments	ICF[a] Screening Visit	First ITI Infusion[b]	Study Visits			Completion/ Termination Visit[c] Success[l], Failure, or 33 Months, Whichever Occurs First
			Visit 1 Wk 2 ± 2 days	Visit 2 Wk 4 ± 2 days	FU Visits Monthly ± 1 week	

d. Adverse events (AEs), concomitant medications, non-drug therapies, and bleeding episodes and their treatment are discussed at these time points but will be continuously monitored in the interim.
e. Includes height and weight at screening and weight at the pre-infusion assessments. Height will be measured every 6 months.
f. Pulse, respiration, supine blood pressure, and temperature to be assessed within 15 minutes prior to start of infusion and 30 ± 5 minutes following infusion.
g. The occurrence of bleeding episodes will be continuously monitored. If bleeding episodes can still be treated with investigational product (IP), treatment has to be recorded in the electronic diary and an hemostatic efficacy rating performed as in Part A. If bypassing agents have to be used, only the type of product, lot numbers and dose will be recorded.
h. A target joint is defined as one in which there have been ≥3 bleeds during the past six-month study period.
i. For laboratory assessments, see Table 9. At all assessments, subjects must not be actively bleeding and assessments should be performed after the longest wash-out period possible without interrupting the ITI therapy schedule. In addition to the assessments shown, clinical laboratory should be performed whenever clinically indicated.
j. If an initial baseline IR from Part A is available: An IR determination will be performed once 2 negative inhibitor titers within a two-month period have been obtained and will be repeated until IR is ≥66% of the initial IR value. The IR should be performed after the longest time interval possible (preferably 48 hours) without undue interruption to the ITI therapy schedule. If the IR is ≥66% of the initial value, ITI should be continued and IR with BAX 855 repeated within 1 month after a wash-out period of at least 84-96 h or the longest time interval possible without undue interruption to the ITI therapy schedule. If IR is again ≥66% of initial value, perform a Completion/Termination Visit. If the BAX 855 IR is <66% of the initial value, ITI therapy should be continued and BAX 855 IR repeated monthly after the longest time interval possible (preferably 48 hours) without undue interruption to the ITI therapy schedule until BAX 855 IR is ≥66% of initial value. ITI should be continued and IR with BAX 855 repeated within 1 month after a wash-out period of at least 84-96 h or the longest time interval possible without undue interruption to the ITI therapy schedule. If IR is again ≥66% of initial value, the Completion/Termination Visit should be performed. If IR remains <66% of initial value, it should be repeated until a maximum of 33 months of ITI has been provided and Completion/Termination Visit performed.
   In case no initial baseline IR of Part A is available, the same procedures as described should be performed. The baseline IR value of 66% is replaced by an IR indicative of an adequate clinical response. An adequate clinical response is defined as pharmacokinetic parameters that permit effective prophylactic treatment of the study subject, including maintenance of FVIII levels above 1%.
k. The IP should be dispensed to provide sufficient treatment for a period of 1 month ± 1 week at the first ITI infusion and at the monthly follow-up visits or according to each institution's standard of care.
l. In case of ITI success, subjects on high-dose ITI will be transitioned to twice weekly prophylaxis (50 IU/kg). FVIII inhibitory and binding antibodies and IR will be assessed prior to each dose adjustment and at the end of the three-month follow-up period. Dose adjustment will be as follows: 1) 100 IU/kg/day for 4 weeks in case the initial subject's ITI therapy consisted of 200 IU/kg/day, 2) 50 IU/kg/day for a further 4 weeks, 3) 50 IU/kg/day every second day for 4 weeks, and 4) 50 IU/kg/day administered twice weekly, adjusted as needed to maintain a FVIII trough level at least 1%, for 3 months.

* Subjects on ITI will follow the monthly procedures for ITI, as specified in the protocol, until ITI success/failure has been established. If ITI is successful,

Table 8
Schedule of Study Procedures and Assessments for Part B (ITI Portion)*

Procedures/ Assessments	ICF[a] Screening Visit	First ITI Infusion[b]	Study Visits			Completion/ Termination Visit[c] Success[l], Failure, or 33 Months, Whichever Occurs First
			Visit 1 Wk 2 ± 2 days	Visit 2 Wk 4 ± 2 days	FU Visits Monthly ± 1 week	

subjects will undergo dose-tapering and then proceed to 3-month visits, as described for Part A, while on optional extended prophylaxis. If ITI fails, subjects have the option to leave the study or further continue ITI adhering to the monthly follow-up visits and procedures.

20.4.2 Clinical Laboratory Assessments in Part B (ITI Portion)

Table 9
Clinical Laboratory Assessments in Part B (ITI portion)[a,*]

			Study Visits			Completion/Termination Visit
Procedures/ Assessments	**ICF Screening Visit**	**First ITI infusion**	**Visit 1 Wk 2 ± 2 days**	**Visit 2 Wk 4 ± 2 days**	**FU visits Monthly ± 1 week**	**Success[i], failure or 33 months, whichever occurs first**
Hematology[b]	X	X			X	X
Clinical Chemistry[c]	X	X			X	X
CD4 Count					X[d]	
FVIII IR[e f]					X	
Immunogenicity[g]	X	X	X	X	X	X
[redacted]						

a. In order to minimize the amount of blood to be drawn at a specific study visit, the required tests can be performed over a couple of days.
b. Hematology assessments include: hemoglobin, hematocrit, red blood cell count, and white blood cell count with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and platelet count. To be measured every 3 months or whenever clinically indicated.
c. 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. To be measured every 3 months or whenever clinically indicated.
d. CD4 count is to be measured every 12 months.
e. An incremental recovery (IR) determination will be performed once 2 negative inhibitor titers within a two-month period have been obtained and will be repeated until IR is ≥66% of initial value or indicative of an adequate clinical response in case no initial IR is available. An adequate clinical response is defined as pharmacokinetic parameters that permit effective prophylactic treatment of the study subject, including maintenance of factor VIIII (FVIII) levels above 1%. See also Table 8 describing the required wash-out period prior to the determination of IR. For IR determination, a pre-infusion blood sample is drawn within 30 minutes of infusion, thereafter 50 ± 5 IU/kg of BAX 855 is infused, followed by a post-infusion blood-draw at 15-30 minutes.
f. Factor VIII assays include: one-stage clotting FVIII activity, FVIII chromogenic activity.

Table 9
Clinical Laboratory Assessments in Part B (ITI portion)[a,*]

			Study Visits			Completion/Termination Visit
Procedures/ Assessments	**ICF Screening Visit**	**First ITI infusion**	**Visit 1 Wk 2 ± 2 days**	**Visit 2 Wk 4 ± 2 days**	**FU visits Monthly ± 1 week**	**Success[i], failure or 33 months, whichever occurs first**

[g] Immunogenicity assessments include: inhibitory antibodies to FVIII, binding antibodies to FVIII, BAX 855 and polyethylene glycol (PEG). Both IgG and IgM binding antibodies will be measured. Positive binding FVIII antibodies will also be tested for subtype IgG antibodies and affinity of subtype IgG antibodies, if needed. Blood draws for immunology assessments have to be performed after the longest time interval possible without interrupting the immune tolerance induction (ITI) therapy schedule. Binding antibodies will be tested using plasma from citrated whole blood. In case of severe hypersensitivity reaction an additional blood sample has to be drawn to test for the presence of IgE antibodies against FVIII and PEG-FVIII. To ensure the clinical management of the subject, clinical decisions to start bypassing agents in addition to BAX 855 may be based on the results of the local laboratory, however, back-up samples must be drawn to have the FVIII inhibitors determined at the central laboratory. If FVIII inhibitors are not confirmed at the central laboratory by a second repeat blood sample, no further bypassing agents may be administered and the subject should discontinue ITI and resume his previous BAX 855 therapy. Subject will be transitioned back to Part A.

[redacted]

[i] In case of ITI success, subjects on high-dose ITI will be transitioned to twice weekly prophylaxis (50 IU/kg). FVIII inhibitory and binding antibodies and FVIII IR will be assessed prior to each dose adjustment and at the end of the three-month follow-up period. Dose adjustment will be as follows: 1) 100 IU/kg/day for 4 weeks in case of initial ITI therapy dose of 200 IU/kg/day, 2) 50 IU/kg/day for a further 4 weeks, 3) 50 IU/kg/day every second day for 4 weeks, and 4) 50 IU/kg/day administered twice weekly, adjusted as needed to maintain a FVIII trough level of at least 1%, for 3 months. Subjects will be monitored for inhibitor recurrence prior to each dose adjustment and at the end of the three-month follow-up period using inhibitory and binding antibodies to FVIII and FVIII recovery measurements. This will coincide with the Completion/Termination Visit. Subjects receiving low dose ITI therapy with 3 x 50 IU/kg weekly will be transitioned to twice weekly 50 IU/kg, adjusted as needed to maintain a FVIII trough level of 1%, for a further 3 months. After this period, a Completion/Termination Visit will be performed.

* Subjects on ITI will follow the monthly procedures for ITI, as specified in the protocol, until ITI success/failure has been established. If ITI is successful, subjects will undergo dose-tapering and then proceed to 3-month visits, as described for Part A, while on optional extended prophylaxis. If ITI fails, subjects have the option to leave the study or further continue ITI adhering to the monthly follow-up visits and procedures.

20.5 Schedules for Surgery

20.5.1 Schedule of Study Procedures for Surgery

Table 10
Schedule of Study Procedures for Surgery

	Preoperative	Intraoperative	Postoperative
Procedure/ Assessment	**~2 h Prior to Surgery**	**In OR**	
Medications and non- drug therapies	X	X	X (daily)
Physical examination	X		X at Day 14 or on discharge[a]
Adverse events	X	X	X
Vital signs[b]	X		X Day 1 and discharge day
FVIII substitution plan	X		
IP treatment	X loading dose	X (as required)	X (as required)
Hemostatic efficacy assessments		X (Table 3)	X at Day 1 (Table 4) X at Day 14 or on discharge[a] (Table 5)
Blood loss	X predicted	X	X
Transfusions		X	X

[a] Whichever is first.
[b] ≤30 min pre, 15 ± 5 min post-dose.

20.5.2 Schedule of Laboratory Assessments for Surgery

Table 11
Schedule of Laboratory Assessments for Surgery

	Preoperative	Intraoperative	Postoperative
Procedure/ Assessment	**~2 h Prior to Surgery**	**In OR**	
FVIII activity (local lab)[a]	X[a] (15 ± 5 min post-FVIII infusion)	(X)[a]	X[a] Within 12 hours after surgery. Subsequently, at least daily (≤30 minutes prior to and 15 ± 5 min post-FVIII infusions).
aPTT (local lab)[b]	X		
Chemistry (optional, local lab)	(X)	(X)	(X)
Hematology (optional, local lab)	(X)	(X)	(X)
Immunogenicity (local and central labs)[c]		(X)[c]	(X)[c]

[a] In addition to timing indicated, may be drawn at any time, including in case of unexpected or excessive bleeding
[b] Surgery may only start if aPTT has normalized.
[c] Required if subject has excessive or unexplained bleeding; FVIII inhibitory and binding antibodies

21. DEFINITIONS

21.1 Definitions of Bleeds[32,33]

21.1.1 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 two.

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

21.1.2 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.

21.2 Definitions of Minor and Major Surgeries

21.2.1 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 (eg, 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 adenotonsillectomy. Examples include[34]:

- 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.

21.2.2 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. DOSING SCHEDULE AND REQUIREMENTS FOR MAJOR SURGERY FOR PART A

22.1 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 study, 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.

For the clinical management of the subject during the perioperative period, the local laboratory can be used. Additional blood draws for testing at the central laboratory are optional in order to minimize the amount of blood to be drawn.

Surgical hemostatic efficacy is to be determined per (Section 11.3, Table 3, Table 4, and Table 5).

22.2 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, 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.

Whenever possible, 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.

22.3 Postoperative Dosing

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:

Whenever possible, 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.

If possible, 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 parameters, ie, 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): it is recommended that the FVIII levels should not fall below 30% (left to the discretion of the investigator depending on the postoperative course)

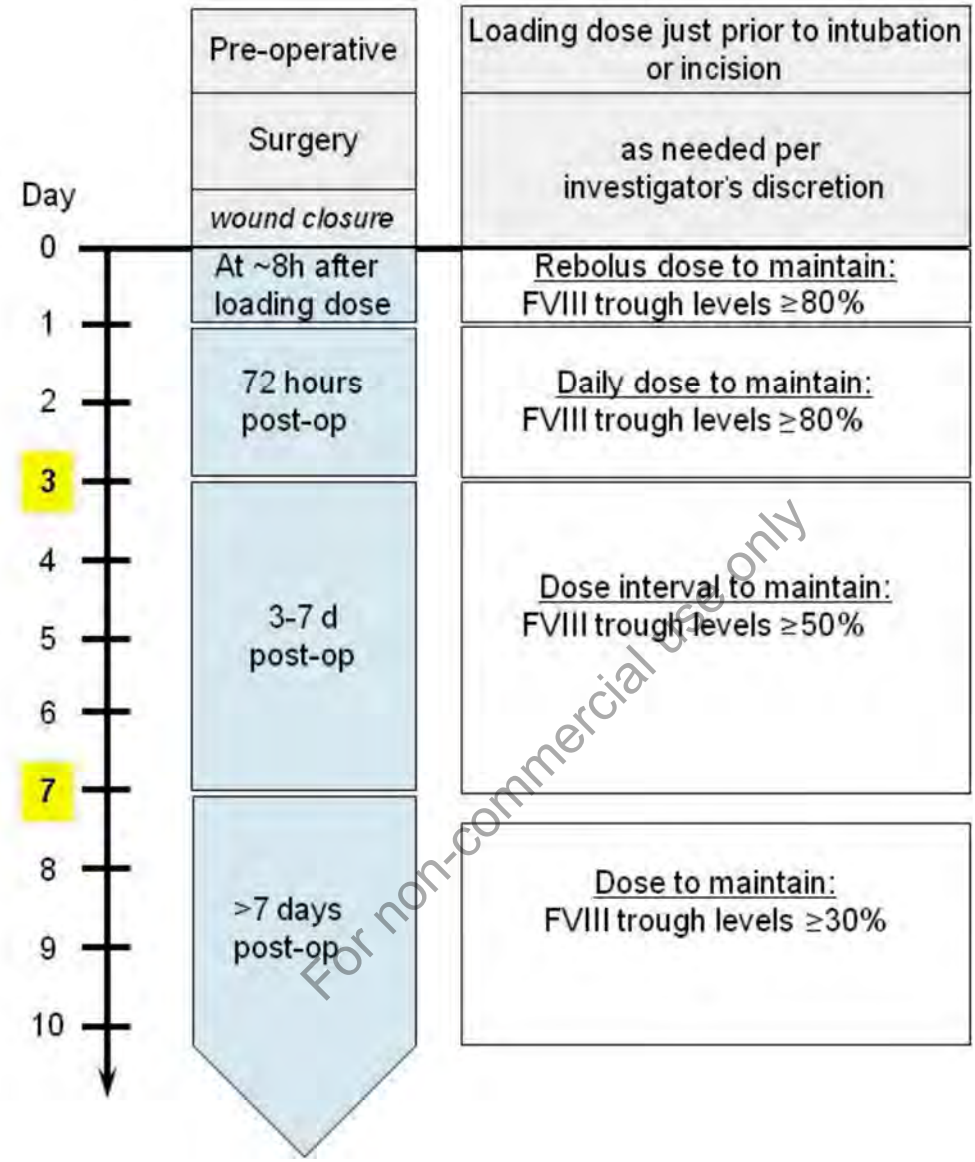
General postoperative treatment recommendations:

- 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%.

Beginning postoperative Day 1 (ie, 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, eg, morning blood draws. At a minimum, a blood sample for FVIII determination must be drawn prior to any supplemental unscheduled FVIII infusion.

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

Figure 3
Dosing Recommendations for Major Surgeries



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24. SUMMARY OF CHANGES

Protocol 261203: AMENDMENT 8 2021 JUN 21

Replaces: AMENDMENT 4: 2018 FEB 08 and AMENDMENT 6 (Turkey): 2019 JUL 01

The primary purpose of this amendment is to update the legal entity for the sponsor to Takeda Development Center Americas, Inc. In addition, new sections have been added regarding Remote Source Document Verification (rSDV) due to COVID-19 and optional extended access to IP.

Specific changes from Protocol Amendments 4 and 6 are described below.

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

2. Throughout the document
   Description of Change: The legal entity for the sponsor was updated to Takeda Development Center Americas, Inc., or sponsor, when applicable
   Reason for Change: To centralize development operations in Takeda Development Center Americas, Inc.

3. Throughout the document
   Description of Change: BAX 855 product code updated to include TAK-660
   Reason for Change: Introduce new naming convention as part of an effort to centralize development operations in Takeda Development Center Americas, Inc.

4. Synopsis, Exclusion Criteria
   Section 9.2 Exclusion Criteria
   Description of Change: The following footnote was added to the exclusion criterion that the subject's weight is less than 5 kg: If a subject is close to weighing 5 kg at screening and will have reached a weight of at least 5 kg at the baseline visit, the subject is eligible for participation.
   Reason for Change: To clarify that the subject´s weight must be 5 kg at baseline

5. Synopsis, Duration
   Synopsis, Planned Duration of Subject Participation
   Section 8.3 Duration of Study Period(s) and Subject Participation
   Supplement 20.1 Study Flow Chart
   Supplement 20.2.1 Detailed Flow Diagram of Study Procedures for Part A, Visit 8
   Supplement 20.3 Schedules for Part A (Main Study), Table 6 and Table 7
   Supplement 20.4 Schedules for Part B (ITI Portion), Table 8 and Table 9.
   Description of Change: New sections 8.3.1 Optional Extension of Access to Investigational Product and 8.3.2 Duration of Optional Extended Access to Investigational Product were added to describe the duration of optional extended access to BAX 855. Additionally, several footnotes were included to clarify procedures to be adhered during optional extended access and in case of ITI
   Reason for Change: Optional extension of access was included to specify the terms and conditions under which subjects who complete the protocol may have continued access to BAX 855

6. Section 1.1 Authorized Representative (Signatory) / Responsible Party
   Description of Change: Updated to the current representative

7. Section 6.1 Description of Investigational Product
   Section 6.4.2 Findings from Clinical Studies
   Section 6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects
   Description of Change: Study descriptions updated to reflect completion statuses
   Reason for Change: Studies were completed

8. Section 8.7.3.3.1 Recommendations for BAX 855 Dose and/or Frequency Adjustments
   Supplement 20.3.1 Schedule of Study Procedures and Assessments for Part A (Main Study)
   Supplement 20.4.1 Schedule of Study Procedures and Assessments for Part B (ITI Portion)
   Description of Change: Amended definition of target joint
   Reason for Change: To be consistent with ISTH 2014 criteria

9. Section 10.3 Screening and Study Visits
   Description of Change: Language updated to clarify screening window
   Reason for Change: To improve protocol clarity

10. Section 10.5 Subject Diary
    Description of Change: Footnote updated to describe use of paper diary in the event that eDiary cannot be made available in subject's native language
    Reason for Change: To improve protocol clarity

11. Section 10.6 Subject Completion/Discontinuation
    Description of Change: Added language indicating that site staff should gain approval for subject to complete Completion Visit
    Reason for Change: To improve protocol clarity

12. Section 12.7.1 Immunogenicity
    Supplement 20.3.2 Clinical Laboratory Assessments in Part A (Main Study)
    Supplement 20.4.2 Clinical Laboratory Assessments in Part B (ITI Portion)
    Description of Change: Updated language relating to immunogenicity assessments
    Reason for Change: To improve clarity of the protocol

13. Section 14 Direct Access to Source Data/Documents
    Description of Change: New Section 14.1 added: Changes Due to COVID-19 Pandemic: Remote Source Document Verification (rSDV). This section adds the provision to include rSDV, if needed, at sites where it is allowed
    Reason for Change: To ensure data quality and integrity and maintain patient safety

14. Section 15.1.1 Final Clinical Study Report
    Investigator Acknowledgement
    Description of Change: Clarified coordinating investigator selection timeline and removed coordinating investigator signature line
    Reason for Change: Coordinating investigator will be selected during study report development

15. Section 20.3.2 Clinical Laboratory Assessments in Part A (Main Study)
    Description of Change: Footnote amended to include [redacted]
    Reason for Change: Updated for consistency

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: TAK-660 (BAX 855) – PEGylated full-length recombinant factor VIII

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

PROTOCOL IDENTIFIER: 261203

CLINICAL TRIAL PHASE 3

AMENDMENT 8 2021 JUN 21

Replaces AMENDMENT 4: 2018 FEB 08
and AMENDMENT 6 (Turkey): 2019 JUL 01

OTHER ID(s)
NCT Number: NCT02615691
EudraCT Number: 2015-002136-40
IND NUMBER: 15299

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

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: TAK-660 (BAX 855) – PEGylated full-length recombinant factor VIII

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

PROTOCOL IDENTIFIER: 261203

CLINICAL TRIAL PHASE 3

AMENDMENT 8 2021 JUN 21

Replaces
AMENDMENT 4: 2018 FEB 08
and AMENDMENT 6 (Turkey): 2019 JUL 01

OTHER ID(s)
NCT Number: NCT02615691
EudraCT Number: 2015-002136-40
IND NUMBER: 15299

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

[redacted]

25-Jun-2021 | 22:02:09 JST

Date

Takeda Pharmaceutical Company Limited

24. SUMMARY OF CHANGES

Protocol 261203: Amendment 4: 2018 FEB 08

Replaces: Amendment 3: 2015 NOV 26

In this section, changes from Protocol Amendment 3 are described and their rationale is given.

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

2. **Synopsis Study Objectives and Purpose: Study Purpose**
   Synopsis: Study Design
   Synopsis, Subject Selection, Inclusion Criteria
   Synopsis, Subject Selection, Exclusion Criteria
   Section 6.3 Population to be Studied
   Section 7.1 Study Purpose
   Section 8.1 Brief Summary
   Section 9.1 Inclusion Criteria
   Section 9.2 Exclusion Criteria
   Description of Change: Substitution of the word "plasma" for "FFP".
   Reason for Change: Per regulations, FFP is one specific type of plasma preparation. The intent is to allow transfusion of all types of plasma components, so the term "plasma" is used to more accurately indicate the intent of the protocol.

3. **Synopsis, Subject Selection, Exclusion Criteria**
   Section 9.2 Exclusion Criteria
   Description of Change: Limiting the total number of ADVATE exposures to 2 EDs total, including prior to enrollment and during the screening period.
   Reason for Change: ADVATE is permitted during the screening period, but no maximum number of exposures was provided. The addition of an explicit limit of ADVATE exposures adds clarity to the subject selection criteria.

4. **Synopsis, Study Design, Secondary Outcome Measures**
   Section 8.2 Overall Study Design
   Section 8.4.2.4 Additional Outcome Measures for ITI
   Section 8.7.3.6 BAX 855 ITI
   Section 9.3 Withdrawal and Discontinuation
   Section 11.4.1 Definition of Success, Partial Success, and Failure
   Supplement 20.2.2 Detailed Flow Diagram of Study Procedures for Part B
   Description of Change: The ITI failure definition is updated to be conditional on the absence of an infection that could explain a failure of inhibitory titers to decrease, in the opinion of the investigator.
   Reason for Change: Recent infection is known to boost inhibitory titers, independent of the effect of ITI. Thus, an ITI course could be deemed a failure for a reason that does not reflect the tolerizing effect of ITI. This change gives investigators the discretion to continue ITI if they deem an infectious cause to be responsible for a failure of inhibitory titers to decrease.

5. **Section 8.3 Duration of Study Period(s) and Subject Participation**
   Description of Change: Wording was added that unless consent is withdrawn, subjects may be contacted by the investigator after the Study Completion Visit for up to 3 months for supplemental clinical information related to the study, if needed.
   Reason for Change: To clarify post-study retrieval of study information from subjects.

6. **Section 10. 5 Subject Diary**
   Description of Change: Wording was added that any site changes/corrections to subject diary data need to be supported by source documentation.
   Reason for Change: To clarify requirements for changes to diaries.

7. **Section 12.7.2.2 FVIII Half-life**
   Supplement 20.2.1 Detailed Flow Diagram of Study Procedures for Part A
   Description of Change: The optional PK assessment is permitted to be performed at Study Visits 1 and 2, in addition to the Baseline Visit.
   Reason for Change: To increase flexibility and convenience for investigators and subjects.

8. **Section 13. 5 Planned Interim Analysis of the Study**
   Description of Change: Wording was added that results of the planned interim analysis will be described in an interim clinical study report.
   Reason for Change: To clarify requirement for interim study report.

9. **Supplement 20.2.1 Detailed Flow Diagram of Study Procedures for Part A**
   Supplement 20.3.1 Schedule of Study Procedures and Assessments for Part A
   Description of Change: Adding a study visit for every 3 months after baseline but before Visit 1.
   Reason for Change: Subjects may receive on-demand treatment only for extended periods of time, and the protocol did not define any follow-up for this situation. Routine follow-up is now included.

10. **Supplement 20.2.2 Detailed Flow Diagram of Study Procedures for Part B**
    Description of Change: Adding required FVIII and immunogenicity assessments monthly if ITI is not started within a month of inhibitor confirmation (Parts A and B).
    Reason for Change: Some investigators prefer to delay initiation of ITI. For safety and immunogenicity assessments, monitoring of the inhibitor is required before ITI is initiated.

11. **Supplement 20.5 Schedules for Surgery**
    Description of Change: Tables added for assessments to be done in case of surgery. The assessments gleaned from the protocol are codified in this new table.
    Reason for Change: Facilitate protocol adherence.

24. SUMMARY OF CHANGES

Protocol 261203: Amendment 3: 2015 NOV 26

Replaces: Original: 2015 MAY 27

In this section, changes from the original version of the Protocol, dated 2015 MAY 27, are described and their rationale is given.

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

2. Throughout the document
   Description of Change: The definition of high-titer inhibitor was changed from ≥5 BU to >5 BU.
   Reason for Change: To comply with standard definition of high-titer FVIII inhibitor which was inadvertently described as ≥ 5 BU in the original protocol.

3. Protocol Title
   Synopsis
   Section 6 Background
   Section 7 Study Purpose and Objectives
   Section 8 Study Design
   Description of Change: Minimally treated patients (MTPs) removed from population to be studied.
   Reason for Change: To comply with a regulatory requirement

4. Section 2
   Description of Change: Wording of first sentence changed to "The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the **Sponsor and/or** ECs**, as applicable**."
   Reason for Change: To comply with UK regulatory requirements.

5. Synopsis, Subject Selection
Section 9 Subject Selection
Description of Changes:
1) Minimally treated patients (MTPs) removed from eligibility;
2) Number of EDs to ADVATE and/or BAX 855 prior to screening changed from equal to or less than (≤) 3 to less than (<) 3 EDs;
3) Gene mutation consistent with severe hemophilia A is optionally supportive in addition to a historical FVIII determination rather than replacing it;
Reason for Change: To comply with regulatory agency requests.

6. Synopsis, Study Design & Subject Selection
Section 6.3 Population to be Studied
Section 8.1 Brief Summary
Section 9.1 Inclusion Criteria
Section 9.2 Exclusion Criteria
Description of Change: The administration of FFP up to a maximum of 2 EDs prior to enrollment is permitted and does no longer constitute an exclusion criterion.
Reason for Change: To consider those situations where still undiagnosed subjects experience a first bleeding episode that is treated with FFP.

7. Synopsis, Exclusion Criteria
Section 9.2 Exclusion Criteria
Description of Change: The following footnote was added to the exclusion criterion that the subject's weight is less than 5 kg: If a subject is close to 5 kg at screening and it is anticipated that he will have reached a weight of at least 5 kg at the baseline visit, the subject is eligibile for participation.
Reason for Change: To clarify that the subject´s weight must be 5 kg at baseline.

8. Synopsis, Exclusion Criteria
Section 9.2 Exclusion Criteria
Description of Change: The following footnote was added regarding systemic immunomodulating drugs: The use of anti-CD20 chimeric monoclonal antibody rituximab with BAX855 during ITI is allowed.
Reason for Change: To comply with a regulatory agency request.

9. Synopsis, Additional inclusion criteria for Part B (ITI)
Section 8 Study Design
Section 9.1.1 Additional inclusion criteria for Part B (ITI)
Description of Change: Inclusion criterion for Part B (ITI) revised as follows: Subject has a confirmed positive high titer inhibitor (> 5.00 BU) or a positive confirmed low titer inhibitor (≥ 0.6 BU) as determined by a central laboratory based on a second repeat blood sample with a) poorly controlled bleeding despite increased BAX855 doses, or b) requires bypassing agents to treat bleeding episodes.
Reason for Change: Regulatory agency request.

10. Synopsis, Additional Exclusion Criteria for Part B (ITI)
Synopsis, Planned Statistical Analysis
Section 8.2 Overall Study Design
Section 12.1.1.1 Serious Adverse Event
Section 12.7.1 Immunogenicity
Section 13.4.1 Primary Outcome Measure
Section 20.2.2 Detailed Flow Diagram of Study Procedures for Part B
Section 20.3.2, Table 7 Clinical Laboratory Assessments in Part A (Main Study)
Description of Change: Clarification provided that in case of a positive inhibitor ≥0.6 BU, a second repeat blood sample needs to be drawn within 2 weeks of study site notification of an inhibitor.
Reason for Change: To specify the time period within which a second repeat blood sample needs to be drawn (for testing at a central laboratory) after study site notification of an inhibitor in compliance with a regulatory agency request.

11. Synopsis, Subject Selection
Section 8.2 Overall Study Design
Description of Change: The number of subjects to be enrolled was changed from ‘at least 110’ to ‘approximately 120’.
Reason for Change: To ensure that at least 100 subjects reach the primary endpoint.

12. Synopsis, Planned Study Period
Section 8.3 Duration of Study Period(s) and Subject Participation
Description of Changes:
1) Duration of Part B: In case of ITI success, a 5-6 month transition period to twice weekly prophylaxis was added including a 3-month follow-up period.
2) The primary completion date for Part B (ITI) was changed from Q4 2022 to Q2 2023. The study completion date for Part B (ITI) was changed from Q2 2023 to Q4 2023.
Reason for Changes:
1) To comply with a regulatory agency request.
2) Timeline changes due to addition of transition period to twice weekly regimen.

13. Section 8.7.2 Administration
Description of Change: The following sentence was added: The actual dose should be based on the weight of the subject determined at the most recent study visit taking into account the allowable dose range.
Reason for Change: Clarification

14. Section 8.7 Investigational Product(s)
Description of Change: Addition of 750 IU/vial, 1500 IU/vial and 3000 IU/vial potencies when available.
Reason for Change: IP update

15. Section 8.7.3.2 BAX 855 Dosing for PK Assessment
Description of Change: This section was newly added..
Reason for Change: To provide guidance on half-life determination in Part A but also Part B as half-life constitutes a criterion for ITI success.

16. Section 8.7.3.4 BAX855 On-demand Dosing for Treatment of Bleeding Episodes
Description of Change: The text regarding therapy for subjects experiencing bleeding episodes in Part B was revised as follows: Rescue therapy for patients who experience acute bleeding episodes during ITI will be treated with the institution's mandated standard of care, which is normally a by-passing agent such as Novoseven (recombinant factor VIIa) or FEIBA (Anti-Inhibitor Coagulant Complex).
Reason for Change: To comply with a regulatory agency request.

17. Synopsis, Secondary Outcome Measures
Section 8.4.2.4 Additional Outcome Measures for ITI
Section 11.4.1 Definition of Success, Partial Success and Failure
Section 13.4.2.4 Additional Outcome Measures for ITI
Description of Change: The definitions of ITI success, partial success and failure were revised as follows:
Success is defined as 1) a persistently negative inhibitor titer < 0.6 BU 2) a FVIII IR ≥ 66% of baseline value following a wash-out period of 84-96 hours and 3) a FVIII half-life of ≥ 6 hours. If no baseline IR is available, the IR value is indicative of an adequate clinical response following a wash-out period of 84-96 hours. An adequate clinical response is defined as pharmacokinetic parameters that permit effective prophylactic treatment of the study, including maintenance of FVIII levels above1%.
Partial success is defined after 33 months of ITI. Two of the following criteria must be met: 1) Inhibitor titer < 0.6 BU (confirmed by a central laboratory with a second blood specimen obtained within 2 months) 2) FVIII IR ≥ 66% (confirmed within a 2-month period) and 3) FVIII half-life ≥6 hours. If no baseline IR is available, the IR value is indicative of an adequate clinical response following a wash-out period of 84-96 hours. An adequate clinical response is defined as, pharmacokinetic parameters that permit effective prophylactic treatment of the study, including maintenance of FVIII levels above1%.
Failure is defined as the failure to meet the criteria for success or partial success within 33 months of ITI therapy OR less than 20% reduction in inhibitor titer, over any 6-month period after the first 3 months of treatment. Subjects who meet failure criteria, i.e decline in the inhibitor titer of < 20% in any 6-month period after the first 3 months of ITI, will have their ITI therapy discontinued.
Reason for Change: Regulatory agency request.

18. Section 8.2 Study Design
Section 8.4.2.4 Additional Outcome Measures for ITI
Section 11.4.1 Definition of Success, Partial Success and Failure
Section 20.2.2 Detailed Flow Diagram of Study Procedures for Part B
Description of Change: The prophylactic dosing regimen employed after ITI success should be adjusted to ensure that the trough FVIII activity level does not fall below 1%.
Reason for Change: To comply with regulatory requests.

19. Section 8.2 Overall Study Design
Section 8.7.3.1 BAX 855 Dosing for IR Assessment at Study Site
Section 8.7.3.6 BAX 855 ITI
Section 12.7.2.1 Incremental Recovery
Section 20.2.2 Detailed Flow Diagram of Study Procedures for Part B
Description of Change: Guidance was added on how subjects will be transitioned from ITI to FVIII prophylaxis, including a monitoring schedule for inhibitor titers.
Reason for Change: Regulatory agency request

20. Synopsis, Investigational Product, Dose and Mode of Administration
Section 8.2 Overall Study Design
Section 8.7.3.1 BAX 855 Dosing for IR Assessment at Study Site
Section 8.7.3.6 BAX 855 ITI
Section 12.7.2.1 Incremental Recovery
Section 20.1 Study Flow Chart
Section 20.2.2 Detailed Flow Diagram of Study Procedures for Part B
Section 20.4.1, Table 8 Schedule of Study Procedures and Assessments for Part B (ITI Portion)
Section 20.4.2, Table 9 Clinical Laboratory Assessments in Part B (ITI Portion)
Description of Change: The following dose adjustments were provided for subjects on high-dose ITI transitioning to a twice weekly prophylaxis following ITI success: 1) 100 ±5 IU/kg/day for the first four weeks, 2) 50 ±5 IU/kg/day for a further four weeks, 3) 50 ±5 IU/kg every second day for four weeks, and 4) 50 ±5 IU/kg administered twice a week, adjusted as needed to maintain a FVIII trough level of 1%, for three months. Subjects will be monitored for inhibitor recurrence prior to each dose adjustment and at the end of the 3-month follow-up period using inhibitory and binding antibodies to FVIII and FVIII recovery measurements. This will coincide with the Completion/Termination Visit. Subjects receiving low dose ITI therapy with 3 x 50 IU/kg weekly will be transitioned to twice weekly 50 IU/kg, adjusted as needed to maintain a FVIII trough level of 1%, for a further 3 months. After this period, a Completion/Termination Visit will be performed.
Reason for Change: To comply with a regulatory agency request.

21. Section 12.7.2.1 Incremental Recovery
Description of Change: Text was added describing the procedure to be followed in case of recurrence of positive inhibitor and/or decrease in the IR (<66% of the initial baseline value) during the transitioning period after successful ITI. A flow chart was also added for this purpose (Figure 2).
Description of Change: To comply with a regulatory agency request

22. Section 12.8 Vital Signs
Section 20.2 Detailed Flow Diagram of Study Procedures
Section 20.3.1 Schedule of Study Procedures and Assessments for Part A
Description of Change: The timepoints for the measurements of vital signs were clarified.
Reason for Change: To ensure that whenever a FVIII is performed, vital signs are determined.

23. Synopsis, Planned Statistical Analysis
Section 13.4.1 Primary Outcome Measure
Description of Change: Clarification provided that inhibitor development will need to be confirmed by a central laboratory based on a second repeat blood sample drawn within 2 weeks of site notification of an inhibitor.
Reason for Change: Clarification

24. Section 8.2 Overall Study Design
Section 12.7.1 Immunogenicity
Section 20.2 Detailed Flow Diagram of Study Protocol
Section 20.2.2 Detailed Flow Diagram of Study Procedures for Part B
Section 20.3.2, Table 7 Clinical Laboratory Assessments in Part A (Main Study)
Section 20.3.2, Table 9 Clinical Laboratory Assessments in Part B (ITI Portion)
Description of Change: To ensure the timely availability of FVIII inhibitor results, the clinical management of the subject may be based on FVIII inhibitors results determined at the local laboratory. An additional blood draw needs to be drawn for testing at the central laboratory each time. In case a FVIII inhibitor is not confirmed by the central laboratory by a second repeat blood sample, the subject will resume his original treatment regimen with BAX 855 and discontinue any treatment with a bypassing agent, if applicable.
Reason for Change: To reduce the turn-around-time and ensure an adequate clinical management of the subject.

25. Section 8.2 Overall Study Design
Section 8.7.3 Description of Treatment
Section 12.7.2.1 Incremental Recovery
Section 20.3.1, Table 6 Schedule of Study Procedures and Assessments for Part A
Description of Change: IR determination will not only be optional at Visit 1 (ED±1) and Visit 3 (ED 15±1) but also at Visit 5 (ED 30±3).
Reason for Change: To reduce the burden of frequent blood draws, some IRs are optional in these pediatric subjects with severe hemophilia A.

26. Section 8.2 Overall Clinical Design
Section 8.4.2.4 Additional Outcome Measures for ITI
Section 8.7.3.1 BAX 855 Dosing for IR Assessment at Study Site
Section 11.4.1 ITI Therapy, Definition of Success, Partial Success and Failure
Section 12.7.2.1 Incremental Recovery
Section 20.2.2 Detailed Flow Diagram of Study Procedures for Part B
Section 20.4.1, Table 8 Schedule of Study Procedures and Assessments for Part B (ITI Portion)
Section 20.4.2, Table 9 Clinical Laboratory Assessments in Part B (ITI Portion)
Description of Change: The following definition for 'adequate clinical response' was added: Adequate clinical response is defined as pharmacokinetic parameters that permit effective prophylactic treatment of the study subject, including maintenance of FVIII levels above 1%.
Reason for Change: Regulatory agency request.

27. Section 8.7.3.1 BAX 855 Dosing for IR Assessment at Study Site
Section 12.7.2.1 Incremental Recovery
Section 20.2 Detailed Flow Diagram of Study Procedures
Section 20.3 Schedules
Description of Change: Clarification provided that in case of low dose prophylaxis consisting of 25 IU/kg BAX 855 weekly, the dose for IR assessment at baseline and during the first 50 EDs to BAX 855 may be lower but not lower than 25 IU/kg BAX 855. Also, in case of on-demand treatment, the initial FVIII IRs may be performed with lower doses, but not lower than 25 IU/kg.
Reason for Change: To ensure continuity in the low dose prophylaxis treatment regimen.

28. Section 12.7.2.1 Incremental Recovery
Section 20.2 Detailed Flow Diagram of Study Procedures
Description of Change: The pre-infusion blood draw for IR determination was changed from "30±5 minutes before start of infusion" to "within 30 minutes of start of infusion".
Reason for Change: To be consistent across the protocol.

29. Section 12.7.2.2 FVIII Half-life
Description of Change: Information was added regarding FVIII half-life assessment in Part B.
Reason for Change: Half-life assessment in Part B was added to comply with Regulatory agency definition of ITI success criteria.

30. Synopsis, Planned Statistical Analysis
Section 13.4.2.4 Additional Outcome Measures for ITI
Description of Change: Separate analyses of data from subjects dosed with the two dosing regimens of 50 IU/kg 3x weekly and 100-200 IU/kg daily will be performed. The analysis of efficacy will be stratified by subjects who received BAX855 as a single agent for ITI and subjects who use BAX855 plus an immune modulatory agent, if applicable.
Reason for Change: Regulatory agency request.

31. Section 10.5 Subject Diary
Description of Change: An infusion record for bypassing agents in Part B (if applicable) will be added to the subject diary.
Reason for Change: To record treatment data on bypassing agents (if applicable)

32. Section 12.7.2 Pharmacokinetics
Description of Change: The following text was added: "If a subject has a central or peripheral venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples. 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."
Reason for Change: To provide guidance for blood sampling for IR or PK determination in case a central or peripheral access device is employed.

33. Section 20.2.2 Study Flow Chart
Description of Change: A flow chart was added (Figure 2) showing the procedure during the transitioning period from successful ITI to twice weekly prophylaxis in case of recurrence of positive inhibitor and/or decrease in the IR (<66% of the initial baseline value).
Reason for Change: Visual aid.

34. Section 22.1 Major Surgery, General
Description of Change: The following text was added: "For the clinical management of the subject during the perioperative period, the local laboratory can be used. Additional blood draws for testing at the central laboratory are optional in order to minimize the amount of blood to be drawn."
Reason for Change: To minimize the amount of blood to be drawn and to ensure an adequate clinical management of subjects during surgery.