CLINICAL STUDY PROTOCOL

NCT Number: NCT02895945

Study Title: A Phase 3, Multicenter, Single-arm, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX802) in Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures

Study Number: 241502

Protocol Version and Date:

Original:	30 Sep 2025
Amendment 1:	03 Feb 2016
Amendment 4:	28 Jun 2017
Amendment 6:	14 Dec 2017

Note: Local protocol amendments are not included.

CLINICAL STUDY PROTOCOL

PRODUCT: BAX802

STUDY TITLE:
A Phase 3, Multicenter, Single-arm, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX802) in Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures

STUDY SHORT TITLE: BAX802 in Congenital Hemophilia A with Inhibitors

PROTOCOL IDENTIFIER: 241502

CLINICAL TRIAL PHASE 3

ORIGINAL: 2015 SEP 30

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: to be determined
IND NUMBER: to be determined

Study Sponsor(s):

Baxalta US Inc.
One Baxter Way
Westlake Village, CA 91362,
UNITED STATES

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna,
AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted], Clinical Development
Baxalta US Inc.

1.2 Study Organization

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

2. SERIOUS ADVERSE EVENT REPORTING

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

ALL SAEs ARE TO BE REPORTED ON THE 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 REQIREMENT.

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:

1. AE, Section 12.1
2. SAE, Section 12.1.1.1
3. Assessment of AEs, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	BAX802
Name(s) of Active Ingredient(s)	Recombinant Porcine Factor VIII
CLINICAL CONDITION(S)/INDICATION(S) [a] Congenital hemophilia A (CHA) patients with inhibitors to FVIII undergoing surgical and other invasive procedures	
PROTOCOL ID	241502
PROTOCOL TITLE	A Phase 3, Multicenter, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX802) in Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures
Short Title	BAX802 in CHA with Inhibitors
STUDY PHASE	Phase 3
PLANNED STUDY PERIOD	
Initiation	2016, FEB
Primary Completion	2017, DEC
Study Completion	2017, DEC
Duration	20 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose To evaluate the efficacy and safety of BAX802 in males with CHA with inhibitors who are undergoing major or minor elective surgical, dental, or other invasive procedures.	
Primary Objective To evaluate the perioperative hemostatic efficacy of BAX802 in male subjects with CHA with inhibitors to human factor VIII (hFVIII) undergoing major or minor elective surgical, dental, or other invasive procedures as determined by the Global Hemostatic Efficacy Assessment (GHEA) score.	
Secondary Objective(s) 1. To determine the safety of BAX802 used in the perioperative setting by assessing: • The development of and change in titer of anti-pFVIII and anti-hFVIII inhibitory antibodies (binding and/or neutralizing), and development of binding antibodies to baby hamster kidney (BHK) proteins • The occurrence of thrombotic events and/or allergic reactions to BAX802 • The occurrence of adverse events (AEs) related to BAX802 • The occurrence of clinically significant changes in vital signs and routine laboratory parameters related to BAX802	

2. To determine the intra- and postoperative blood loss at the end of surgery, compared to the estimated volume of expected average and maximum blood loss in a comparable healthy individual as predicted preoperatively by the investigator/surgeon
3. To determine the daily and total weight-adjusted administration of BAX802 per subject
4. To determine the blood product utilization
5. To determine the occurrence of bleeding episodes during the intra- and postoperative periods and additional need for surgical intervention
6. To evaluate any intercurrent, unrelated bleeding episodes in the postoperative period.

STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy and Safety
Control Type	No control
Study Indication Type	Treatment
Intervention model	single-group
Blinding/Masking	Open-label
Study Design	This study is a Phase 3, prospective, open-label, uncontrolled, multicenter study to evaluate the efficacy and safety of BAX802 in at least 10 evaluable male subjects with CHA with inhibitors to hFVIII who are undergoing major and minor surgical, dental or other invasive procedures. At least 5 of the procedures must be major surgeries in 5 evaluable subjects.
Planned Duration of Subject Participation	The duration of subject participation depends on the nature of the invasive procedure: it will run from the signing of the informed consent until completion of the End of Study Visit (at least 6 weeks post-surgery [Day 0]).

Primary Outcome Measure

The primary outcome measure is the GHEA score, which is composed of 3 individual ratings:

- Assessment of intraoperative hemostatic efficacy of BAX802 performed by the operating surgeon
- Assessment of postoperative hemostatic efficacy of BAX802 at postoperative Day 1 (approximately 24 hours after surgery) performed by the operating surgeon
- Assessment of postoperative hemostatic efficacy of BAX802 at Day 14, performed by the investigator.

The scores of each of the 3 individual ratings described above, will be added together to form a GHEA score

Secondary Outcome Measure(s)

Efficacy

1. Intra- and postoperative blood loss compared to the estimated volume of expected average blood loss and expected maximum blood loss in a comparable healthy individual as predicted preoperatively by the investigator/surgeon at the following time points:
   - Intraoperative, at the end of surgery
   - Postoperative Day 1, approximately 24 hours after surgery
   - Postoperative Day 14
2. Daily and total weight-adjusted administration of BAX802 per subject
3. Volume of blood, red blood cells, platelets, and other blood products transfused
4. Occurrence of bleeding episodes during the intra- and postoperative periods and additional need for surgical intervention
5. Efficacy of the treatment of intercurrent, unrelated bleeding episodes in the postoperative period.

Safety

1. Development of, and changes to, the titer of inhibitory and binding antibodies to recombinant porcine factor VIII (rpFVIII)
2. Development of, and changes to, the titer of inhibitory and binding antibodies to hFVIII
3. Development of binding antibodies to BHK proteins
4. Occurrence of thrombotic events
5. Incidence of severe allergic reactions (eg, anaphylaxis)
6. Incidence of other IP-related AEs
7. Incidence of clinically significant changes in vital signs and routine laboratory parameters (hematology, clinical chemistry)

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form:** Injectable Reconstituted Solution **Dosage frequency:** PRN = as needed **Mode of Administration:** intravenous bolus
SUBJECT SELECTION	
Targeted Accrual	Enroll 10 evaluable subjects
Number of Groups/Arms/Cohorts	1 arm: 10 evaluable adult male subjects (≥ 18 to ≤ 65 years old) with CHA with inhibitors to FVIII undergoing surgical and other invasive procedures for efficacy and safety evaluation

Inclusion Criteria

1. Subject is ≥ 18 to ≤ 65 years old at the time of screening
2. Subject has provided signed informed consent
3. Subject has severe (FVIII level < 1%) or moderately severe (FVIII level ≤ 2%) CHA with inhibitors to human FVIII, as tested at screening at the central laboratory
4. Subject requires elective surgery or other invasive procedures
5. Subject is not currently receiving ITI therapy
6. Subject has a Karnofsky performance score of ≥ 60
7. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm3 at screening
8. Subject is hepatitis C virus negative (HCV-) by antibody or polymerase chain reaction (PCR) testing; or HCV+ with chronic stable hepatitis disease
9. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

1. The subject requires emergency surgery
2. The subject's weight is < 35 kg or > 120 kg
3. Clinically symptomatic liver disease (eg, ≥ 5 X upper limit of normal alanine aminotransferase [ALT], as confirmed by central laboratory at screening, clinical evidence of portal hypertension, severe hypoalbuminemia or a documented prothrombin time/international normalized ratio [PT/INR] > 1.5)
4. Clinically symptomatic renal disease (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening
5. Anti-porcine inhibitor > 10 Bethesda units (BU) prior to surgery
6. Platelet count < 100,000/µl
7. Active condition of coagulation disorder such as von Willebrand disease
8. Planned use of α-interferon with or without ribavarin for HCV infected patients or planned use of a protease inhibitor for HIV-infected patients. Patients currently taking any of these medications for ≥ 30 days are eligible
9. Known hypersensitivity to rpFVIII, or hamster or murine proteins
10. Subject has been exposed to an IP 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
11. Unable to tolerate quantity of blood to be drawn for protocol procedures
12. Subject is a family member or employee of the investigator

STATISTICAL ANALYSIS

Sample Size Calculation

The sample size of 10 evaluable male subjects, 5 of which must have major surgery as defined in the protocol, was chosen to provide sufficient evidence of safety and effectiveness for this indication and is not based on statistical considerations.

Planned Statistical Analysis

Datasets and Analysis Cohorts

The safety analysis set (SAS) will be comprised of all subjects who received any amount of BAX802. The full analysis set (FAS) will comprised of all subjects with at least one available hemostatic assessment. The per-protocol analysis set (PP) will comprise all subjects with available perioperative hemostatic efficacy assessed by:

i) the operating surgeon within 60 minutes post-surgery

ii) postoperative hemostatic control assessed by the operating surgeon postoperatively at 24 hours, and

iii) postoperative hemostatic control assessed by the investigator during Day 14.

Only subjects who meet all study entry criteria and who have no major protocol violations that might impact hemostatic efficacy assessments will be included in the PP analysis set.

Primary Outcome Measure

The primary efficacy measure will be the overall assessment of hemostatic efficacy assessed intraoperatively by the surgeon and postoperatively by the investigator (hemophilia physician) at postoperative Day 1 (ie, the day following the day of surgery) and at postoperative Day 14 visit, and will be summarized by the GHEA score and rated "excellent", "good", "moderate" and "none".

A treatment success will be defined as a rating of excellent and/or good.

Point estimates and corresponding two-sided exact confidence intervals (CIs) at the 90% confidence level will be calculated for the rate of hemostatic efficacy assessments with excellent/good outcome.

The primary efficacy analysis will be based on the FAS. As a supportive analysis, the same calculations will also be carried out on the PP population.

Secondary Outcome Measures

Secondary hemostatic efficacy analysis:

Descriptive statistics will be used to summarize the actual blood loss and transfusion requirements. The summary of average daily and total weight-adjusted doses (average through postoperative Day 14) of BAX802 per subject as well as the occurrence of bleeding episodes will be provided using descriptive statistics. For intercurrent, unrelated bleeding episodes in the postoperative period, descriptive statistics will be used to summarize the overall hemostatic efficacy rating at 24 ±2 hours after initiation of treatment and at resolution of bleed. The secondary efficacy analysis will be performed on the FAS only.

Safety Analysis

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by presenting the number and percentage of subjects having any AE, having an AE in each system organ class, and having each individual AE as reported by preferred term. In the summaries, AEs will be counted only once per patient. If a patient reports the same AE more than once, it will be counted with its worst severity and closest relationship to the study product.

The number of subjects who experienced serious adverse events (SAEs) and the number of SAEs will be tabulated. In addition, the number of subjects who experienced AEs related to IP and the number of IP related AEs will be tabulated and subcategorized for thrombotic events, inhibitory and total binding antibodies to rpFVIII and hFVIII, and binding antibodies to BHK proteins.

An overview table for AEs will be provided, presenting the number of AEs, the number of subjects with AEs and the corresponding percent of subjects in total, and by seriousness and relationship to study treatment. An additional summary table will present the total number of (mild, moderate, severe) AEs by system organ class and preferred term with relationship to IP.

Summary statistics over time will be presented for the continuous laboratory parameters. Descriptive statistics of changes from baseline (Day 0 - prior to surgery) by study visits will also be presented.

A frequency table of results of categorical laboratory parameters will be produced. Furthermore, laboratory abnormalities will be analyzed by shift tables where each subject will be counted only once with the worst grade in the summary tables.

Vital signs assessments as well as the corresponding changes from baseline will be summarized descriptively at each scheduled assessment.

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AICC	anti-inhibitor coagulant complex
ALT	alanine aminotransferase
aPCC	activated prothrombin complex concentrate
B19V	parvovirus B19
BHK	baby hamster kidney
BU	Bethesda units
CI	confidence interval
CHA	Congenital Hemophilia A
CRF	case report form
CRO	Contract Research Organization
EC	ethics committee
EBL	estimated blood loss
eCRF	electronic case report form
EDC	electronic data capture
FAS	full analysis Set
GCP	Good Clinical Practice
GHEA	Global Hemostatic Efficacy Assessment
HAV	hepatitis A virus
HBV	hepatitis B virus
Hct	hematocrit
HCV	hepatitis C virus
HEV	hepatitis E virus
hFVIII	human factor VIII
HIV	human immunodeficiency virus
IB	Investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IP	investigational product
IPC	intermittent pneumatic compression
iSMC	internal Safety Monitoring Committee
ITI	immune tolerance induction

Abbreviation	Definition
LMWH	low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
NMC	Non-medical complaint
OR	operating room
PCR	polymerase chain reaction
pFVIII	porcine factor VIII
PP	Per Protocol (analysis set)
PRN	"pro re nata" (as needed)
PT/INR	prothrombin time/international normalized ratio
PV	plasma volume
rhFVIII	recombinant human factor VIII
rpFVIII	recombinant porcine factor VIII
SAE	serious adverse event
SAER	serious adverse event report
SAP	statistical analysis plan
SAS	safety analysis set
SIC	subject identification code
TGA	thrombin generation assays
VIIa	activated factor VII
WFH	World Federation of Hemophilia

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

The investigational product (IP), BAX802, is a recombinant form of porcine factor VIII (rpFVIII) from which the B domain has been deleted. Deletion of the B domain does not affect the safety or efficacy of this recombinant form of human factor VIII (rhFVIII) in the treatment of hemophilia A. BAX802 (rpFVIII) is being developed for the perioperative management of hemostasis in subjects with congenital hemophilia A (CHA) with inhibitors to human factor VIII (hFVIII) undergoing surgical or other invasive procedures. This rpFVIII was approved by the United States Food and Drug Administration (FDA) in 2014 for the treatment of bleeding episodes in adults with acquired hemophilia A (AHA; non hemophilia subjects developing spontaneous autoantibody inhibitors to hFVIII) under the trade name OBIZUR®.

6.2 Clinical Condition/Indication

Congenital hemophilia A is a congenital bleeding disorder caused by a deficiency or complete absence of coagulation factor VIII (FVIII) [1] and is referred to as CHA in order to differentiate it from AHA, which is a rare autoimmune disease with different bleeding patterns caused by immunoglobulin G antibodies that bind to specific domains on the FVIII molecule, in a person with a negative personal or family history of a coagulopathy.[2]

Overall, CHA accounts for about 80% of hemophiliacs. It affects all ethnic populations and its prevalence varies among different countries, but is estimated at a rate of 3 to 20 cases per 100,000 population. The World Federation of Hemophilia (WFH) has estimated the total number of hemophilia cases at about 500,000 universally, of which one-third are diagnosed. The tendency to bleed in these subjects correlates with the plasma level of FVIII. This lifelong disorder has three clinical phenotypes (severe, moderate, and mild) that correlate with FVIII levels in plasma (< 1%, 1 - 5%, and 5 - 30%, respectively).[3]

Subjects with hemophilia A typically develop recurrent bleeding episodes. The most effective approach for treatment of acute bleeding episodes in subjects with hemophilia A is hFVIII replacement therapy.[4,5] However, a major complication in the treatment of subjects with A is the development of neutralizing antibodies (inhibitors) to hFVIII, which impair the efficacy of replacement therapy with hFVIII concentrates. Inhibitor development occurs more frequently among patients with severe or moderately severe hemophilia, and approximately 30% of patients with severe CHA develop inhibitors.

In CHA patients with high-responding inhibitors, standard replacement therapy with FVIII concentrates is usually ineffective, resulting in poor control of hemorrhagic episodes. This in turn increases the risk of morbidity, mortality, orthopedic complications and disability, as well as reduced quality of life, compared with patients without inhibitors.[6] Patients with CHA with inhibitors are also at risk of perioperative bleeding complications, since replacement of the missing coagulation factor is ineffective, presenting a therapeutic challenge in elective or emergency surgery.[7]

Currently Available Treatments and Unmet Medical Need

In CHA patients with transient, low-responding and/or low-titers (< 5 Bethesda units [BU]/mL) inhibitors, increased doses of FVIII may be sufficient to overcome the inhibitor and provide hemostasis. In CHA patients with high-responding inhibitors (> 5 BU/mL), standard replacement therapy with FVIII concentrates is usually ineffective, resulting in poor control of hemorrhagic episodes.

Alternative therapies are required for subjects with inhibitors who no longer respond to hFVIII replacement therapy. Recombinant activated factor VII (rFVIIa, NovoSeven®) and FEIBA (Factor VIII inhibitor bypassing activity; anti-inhibitor coagulant complex [AICC]) bypass the normal coagulation cascade and hence the FVIII inhibitors, and are therefore referred to as bypassing agents. Although these agents are able to manage bleeding in the presence of inhibitors, they do not attempt to restore the normal pathways of hemostasis, but instead boost thrombin generation despite a lack of platelet-surface FVIIIa–FIXa ('tenase') activity.[6] The measurement of levels of factor VIIa in the subject's plasma cannot be used as a clinically relevant surrogate marker and does not correlate with clinical outcome. Without an adequate biomarker, the dosage and treatment schedule cannot be clearly defined.[8] In addition, the response to rFVIIa treatment may be inconsistent both from subject to subject and between different bleeds in the same subject. Because FEIBA is a human plasma fraction containing several coagulation factors, it has the potential to transmit human pathogens and may also cause thromboembolic events. Since the plasma fraction also contains hFVIII, it has been associated with a rise in hFVIII antibodies in approximately 20% of subjects.[9] Moreover, as with rFVIIa, there is no validated biomarker that correlates with the clinical outcome with FEIBA treatment, although both thrombin generation assays (TGA) and whole blood viscoelastic assays have been evaluated for this purpose with some success.[10]

The ultimate goal of treatment for these patients is eradication of the inhibitor through immune tolerance induction (ITI), which involves frequent and long-term administration of factor concentrates in an attempt to build tolerance in the immune system to FVIII or factor IX, and thus restore responsiveness to factor replacement therapy. However, ITI fails in approximately 30% of inhibitor patients with CHA.[6]

There is therefore a clinical need for an effective hemostatic agent for use in subjects with CHA who have inhibitors to hFVIII, and which allows monitoring of hemostatic efficacy based upon measurement of plasma FVIII activity levels, thus facilitating early determination of clinical benefit and the patient's clinical status.

6.3 Population To Be Studied

The study population will comprise 10 male subjects with CHA with inhibitors to hFVIII undergoing major or minor elective surgical, dental, or other invasive procedures. Adult (≥ 18 and ≤ 65 years) male subjects will be considered to be eligible provided that they satisfy all of the inclusion criteria listed in Section 9.1 and none of the exclusion criteria listed in Section 9.2.

6.4 Findings from Nonclinical and Clinical Studies

6.4.1 Finding from Nonclinical Studies

Nonclinical studies were performed with rpFVIII to demonstrate hemostatic activity in two animal models of hemophilia A (mice and dogs), local and systemic tolerance in a range of doses in single or repeat dose toxicology studies in monkeys, pharmacokinetics (PK) in dogs and monkeys, and immunogenicity in mice and monkeys.

Compatibility with the usual injection materials (needles, plastic syringes, and butterfly infusion needles with tubing) has been demonstrated. Studies in monkeys demonstrated the tolerability of repeated single daily injections of rpFVIII at doses up to 1000 U/kg, with injections at each dose level given once daily for 7 days. In two animal models of hemophilia A (mice and dogs), the hemostatic activity of rpFVIII was studied in comparison with Hyate:C. The rpFVIII was found to be efficacious in a dose-related fashion in controlling the bleeding associated with a standardized hemorrhagic insult. No animal studied was observed to have had an acute reaction to the injection of rpFVIII.

6.4.2 Finding from Clinical Studies

The safety and efficacy of rpFVIII was explored in four clinical trials prior to marketing approval:

- OBI-1-101: a Phase I, multicenter, randomized, double-blinded, double-dummy, parallel-group, comparison of the safety, tolerance, and PK study of rpFVIII versus Hyate:C was conducted.[11]
- OBI-1-201: a Phase II, prospective, open-label, non-comparative study was conducted to assess the hemostatic activity of rpFVIII. Eligible subjects had a clinical diagnosis of hemophilia A with inhibitors to hFVIII, an anti-pFVIII inhibitor antibody titer < 20 BU at screening, and an uncomplicated joint or soft tissue bleed, or other non-life threatening and non-limb threatening bleeding episode.[12]
- OBI-1-301: a multicenter, open-label, single-cohort, prospective, Phase II/III study of rpFVIII in subjects with acquired hemophilia to determine the hemostatic efficacy and safety of rpFVIII in the control of serious bleeding episodes.[13]
- OBI-1-302: a prospective, non-randomized, open-label study designed to assess treatment of serious bleeding episodes with rpFVIII in subjects with CHA who had developed anti-hFVIII inhibitors; this study was terminated by the sponsor after one subject was treated for administrative reasons, not due to safety or lack of efficacy concerns.

In all clinical studies, rpFVIII was generally well tolerated. There were no drug-related AEs reported in subjects who received rpFVIII in the Phase I study. One subject in the Phase II study (OBI-1-201) experienced pruritus (that resolved with diphenhydramine) that was possibly related to study drug. This AE occurred during the first bleeding episode, but the subject did not have a reaction during a second rpFVIII treated bleeding episode. In the Phase I and Phase II studies, no AEs led to treatment interruption, discontinuation from the study, or death. Vital signs, laboratory values, medical history and physical examination findings were within normal parameters for both studies and raised no safety concerns.

In the Phase II study (OBI-1-201), the ITT Population consisted of nine male subjects with CHA and with an inhibitor antibody to hFVIII. Six of the subjects (67%) were black and 3 subjects (33%) were Caucasian. The mean age of the subject population was 23.7 years (Range: 14 to 34). The primary efficacy objective of the study was to evaluate the hemostatic efficacy of rpFVIII in the treatment of non-life/non-limb threatening bleeds in subjects with CHA and inhibitors.

A total of 25 bleeds in 9 subjects were treated with rpFVIII and all bleeds were successfully controlled with 8 or less injections of rpFVIII. The median number of rpFVIII injections administered per bleeding episode was 1.0 (Range: 1 to 8) and the median time from bleeding onset to treatment was 5.67 hours (range: 1.5 to 20.0 hours). Across all bleeding episodes the median total dose of rpFVIII per bleeding episode was 224.1 U/kg (range: 50.0 to 1066.4 U/kg). The median initial Treatment Dose (including the Loading Dose if applicable), was 159 U/kg (Range: 50 to 576 U/kg) and resulted in a median increase of FVIII plasma level of 16 % with the 1-stage clotting assay (Range: 0.5 to 427 %) and a median increase of 17% with the chromogenic assay (Range: 0 to 248 %). Twenty of the 25 (80%) bleeds were controlled within 6 hours having been administered one Treatment Dose of rpFVIII. For those 20 bleeds controlled with 1 Treatment Dose (including the Loading Dose if applicable), the median dose was 200.8 U/kg. rpFVIII was well tolerated and of the reported AEs (n=61) only 18 were considered treatment emergent. Two subjects reported an AE that was possibly related to study drug. One AE of itching/pruritus during the first bleeding episode but without reaction during a second rpFVIII treated bleeding episode. The second AE was a report of increased ALT and AST, possibly associated with a confirmed Hepatitis C infection, while it was uncertain whether the corresponding blood sample was taken before or after rpFVIII administration. Three subjects suffered treatment emergent SAEs but none were considered related to study drug. No reported AE led to treatment interruption, discontinuation from the study or death. Eight out of 9 (8/9, 89%) subjects developed anti-pFVIII antibodies following exposure to rpFVIII. In subjects that received repeated rpFVIII treatment, higher anti-pFVIII titers did not affect efficacy or safety and no increase in AEs or bleeding episodes were reported in the subjects with the highest titers. Regardless of the observed anti-pFVIII titers at pre-treatment or the obtained FVIII recovery values after treatment initiation, all bleeding episodes were successfully controlled. Analyses of baby hamster kidney (BHK; host cell line) antibody levels indicated that no subjects produced detectable levels of antibodies against BHK.

In the prospective, open-label trial (OBI-1-301), the efficacy of rpFVIII for the treatment of serious bleeding episodes in subjects with AHA was investigated. The trial was conducted in 18 Caucasian, 6 African-American, and 5 Asian subjects diagnosed with AHA, having auto-immune inhibitory antibodies to hFVIII, and experiencing serious bleeding episodes that required hospitalization. Subjects with a prior history of bleeding disorders other than AHA, anti-pFVIII antibody titer > 20 BU, or in whom the bleeding episode was judged likely to resolve on its own, were excluded. One subject was considered evaluable at study entry; however, it was later determined that this subject did not have AHA, leaving 28 subjects evaluable for efficacy.

Of the 28 subjects evaluable for efficacy, all subjects had a positive response to treatment for the initial bleeding episodes at 24 hours after dosing. A positive response was observed in 95% (19/20) of subjects evaluated at 8 hours and 100% (18/18) at 16 hours. In addition to response to treatment, the overall treatment success was determined by the investigator based on his/her ability to discontinue or reduce the dose and/or dosing frequency of rpFVIII. A total of 24/28 subjects (86%) had successful treatment of the initial bleeding episode. Of those subjects treated with rpFVIII as first-line therapy, defined as no immediate previous use of anti-hemorrhagic agents prior to the first rpFVIII treatment, 16/17 subjects (94%) had eventual treatment success reported. Eleven subjects were reported to have received anti-hemorrhagics (eg. rFVIIa, activated prothrombin-complex concentrate, tranexamic acid) prior to first treatment with rpFVIII. Of these 11 subjects, 8 had eventual successful treatment (73%). No related serious adverse reactions occurred. Non-serious adverse events related to treatment were noted and assessed by the investigator in 6/29 subjects (20.7%). One subject had mild tachycardia, hypotension and constipation. One subject had 2 instances of mild PICC line occlusion. One subject had a mild hypofibrogenemia and 1 subject had moderate mental status changes. All of these adverse effects completely resolved. Two subjects developed anti-porcine FVIII inhibitors after infusion of study drug (range 8 - 51 BU) and were discontinued from treatment; however both subjects had a positive response to treatment at the 24 hour primary endpoint assessment. An investigation was conducted by the sponsor and, in summary, the 2 incidences of anti-porcine FVIII inhibitors were considered related to rpFVIII treatment, while the other non-serious treatment-related adverse events were considered as unlikely to be related to rpFVIII. Anti-porcine FVIII inhibitors were detected prior to infusion in 10/29 patients (range 0.8 - 29 BU). All of these subjects had a positive response at 24 hours post-rpFVIII first infusion. No anti-BHK antibodies were observed in any of the 29 treated subjects.

At the time of OBIZUR® marketing approval, the clinical trial data indicated that rpFVIII was well tolerated and had demonstrated effectiveness in the control of bleeding in study subjects. No post-marketing adverse reactions had been reported per the most recent Company Core Data Sheet for OBIZUR® (22 July 2015).[14]

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

Porcine factor VIII (Hyate:C), derived from porcine plasma, had been used successfully starting in the 1980s to achieve hemostasis in the presence of anti-hFVIII inhibitors, as the antibodies generally have low immunological cross-reactivity with porcine factor VIII (pFVIII).[15] However, the number of hemophilia A subjects who were appropriate candidates to receive Hyate:C was limited by the degree to which their anti-hFVIII antibodies cross-reacted with pFVIII and the presence of any anti-pFVIII inhibitors. While a median inhibitor cross-reactivity observed to porcine VIIIC was only 15%, an absent, intermediate, or brisk specific anti-porcine anamnestic response was observed in 29%, 40%, and 31% of patients, respectively.[16] The commercial production of Hyate:C was discontinued in 2005 due to problems with sourcing suitable porcine plasma, but not due to any safety or efficacy concerns.

BAX802 is a B-domain deleted rpFVIII glycoprotein which is being developed for the perioperative management of hemostasis in subjects with CHA with FVIII inhibitors undergoing surgical or other invasive procedures. B-domain deleted rpFVIII glycoprotein has been extensively studied. BAX802 (as marketed OBIZUR®) is not currently indicated for the treatment of CHA.[17]

OBIZUR® was approved based on the safety and efficacy data from 28 subjects with AHA treated with B-domain deleted rpFVIII glycoprotein in the phase 2/3 open-label clinical study OBI-1-301. The safety, hemostatic activity, and PK profile of B-domain deleted rpFVIII glycoprotein was also supported by results of an open-label phase 2 study in patients with CHA with inhibitors (CSR OBI-1-201), and a randomized phase 1 study comparing B-domain deleted rpFVIII glycoprotein with a plasma-derived porcine factor VIII (CSR OBI-1-101).

The data supported the use of B-domain deleted rpFVIII glycoprotein to treat serious bleeding episodes in AHA patients (Section 6.4.2). It was demonstrated that B-domain deleted rpFVIII glycoprotein provides benefit to AHA patients who are unresponsive to alternative agents with an improved dosing algorithm. It was possible to monitor hemostatic efficacy based upon measurement of plasma FVIII activity levels, thus facilitating early determination of clinical benefit and the patient's clinical status. An additional benefit to the patient was that it was possible to adjust the dose based on the FVIII levels rather than follow fixed dosing, ensuring that adequate doses were administered to achieve hemostasis.

The most frequently reported adverse reaction in patients with AHA was the development of inhibitors to pFVIII.[17]

Overall, efficacy and safety clinical data for OBIZUR supported a favorable benefit/risk determination for the proposed indication of treatment of bleeding episodes in adults with AHA.

These data support the investigation of efficacy and safety of BAX802 in subjects with CHA with inhibitors undergoing surgical or other invasive procedures.

6.6 Compliance Statement

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

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is to evaluate the efficacy and safety of BAX802 in males with CHA with inhibitors who are undergoing major or minor elective surgical, dental, or other invasive procedures.

7.2 Primary Objective

The primary objective of the study is to evaluate the perioperative hemostatic efficacy of BAX802 in male subjects with CHA with inhibitors to hFVIII undergoing major or minor elective surgical, dental, or other invasive procedures as determined by the Global Hemostatic Efficacy Assessment (GHEA) score.

7.3 Secondary Objectives

The secondary objectives of the study are to:

1. To determine the safety of BAX802 used in the perioperative setting by assessing:
    - The development of and change in titer of anti-pFVIII and anti-hFVIII inhibitory antibodies (binding and/or neutralizing), and development of binding antibodies to BHK proteins
    - The occurrence of thrombotic events and/or allergic reactions to BAX802
    - The occurrence of AEs related to BAX802
    - The occurrence of clinically significant changes in vital signs and routine laboratory parameters related to BAX802
2. To determine the intra- and postoperative blood loss at the end of surgery, compared to the estimated volume of expected average and maximum blood loss in a comparable healthy individual as predicted preoperatively by the investigator/surgeon
3. To determine the daily and total weight-adjusted administration of BAX802 per subject
4. To determine the blood product utilization
5. To determine the occurrence of bleeding episodes during the intra- and postoperative periods and additional need for surgical intervention
6. To evaluate any intercurrent, unrelated bleeding episodes in the postoperative period.

8. STUDY DESIGN

8.1 Brief Summary

This study is a Phase 3, uncontrolled, open-label, single-group, multicenter study to determine the safety and efficacy of BAX802 in 10 male subjects with CHA with inhibitors to hFVIII who are undergoing major or minor elective surgical, dental, or other invasive procedures.

8.2 Overall Study Design

This study is a Phase 3, prospective, open-label, uncontrolled, multicenter study to evaluate the efficacy and safety of BAX802 in at least 10 evaluable male subjects with CHA with inhibitors to hFVIII who are undergoing major and minor surgical, dental or other invasive procedures. At least 5 of the procedures must be major surgeries in 5 evaluable subjects (see Section 8.2.1).

The dose and frequency of BAX802 during the preoperative, intraoperative, and postoperative periods should follow a substitution plan provided by the investigator prior to surgery and adjusted based on regular FVIII activity measurements. The regimen will depend on the type of surgery performed and the intensity of the hemostatic challenge.

Elective surgical procedures will prospectively be defined as major or minor by the investigator/surgeon and agreed with the medical director/designee, based on the protocol guidance and definitions and in consideration of each subject's characteristics. Emergency surgeries are not in the scope of this study. Subjects may undergo more than 1 surgery or 2 parallel surgeries, such as bilateral knee replacement, however, in these cases prior approval by the sponsor is required.

The study will be conducted globally and will be divided into 5 periods: Screening, Preoperative, Intraoperative, Postoperative, and End of study (Table 8).

The overall study design is illustrated in Figure 1.

8.2.1 Types of Interventions

Elective procedures will prospectively be defined by the investigator/surgeon as major or minor based on the definitions and examples provided in Section 8.2.1.1 and Section 8.2.1.2 taking into consideration each individual patient's characteristics and agreement with the sponsor.

8.2.1.1 Major Surgeries

Major surgeries include surgeries that require moderate or deep sedation, general anesthesia, or major conduction blockade for patient comfort. This 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 (> 500 mL) or blood loss into a confined anatomical space. Several tooth extractions or extraction of the third molar are generally considered as major. Examples include:

- bone fixation for fracture
- hip and knee replacement (arthroplasty)
- arthrodesis (joint fusion)
- open synovectomy
- osteotomy
- liver biopsy
- pseudotumor removal
- hardware removal (plates, intramedullary nails)

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

8.2.1.2 Minor Surgeries

Minor surgeries include surgeries that can be safely and comfortably performed on a patient who has received local or topical anesthesia, without more than minimal preoperative medication or minimal preoperative medication or minimal intraoperative sedation. The estimated total blood loss should be < 500 mL and the likelihood of complications requiring hospitalization or prolonged hospitalization should be remote. It refers to interventions such as removal of skin lesions, arthroscopy, minor dental procedures or dental extractions. Examples include:

- removal of skin lesions
- 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

- arthroscopy
- 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

8.2.2 Dose Selection Rationale

Background

This is a Phase 3, open label study of the efficacy and safety of B-domain deleted rpFVIII (BAX802) in the perioperative management of hemostasis in subjects with CHA who have inhibitors and are undergoing surgical or other invasive procedures. The rpFVIII temporarily replaces the inhibited FVIII that is needed for effective hemostasis in CHA patients who have developed inhibitors to hFVIII. The principle of using pFVIII is based on its low cross-reactivity with anti-hFVIII antibodies due to sequence variations between human and pFVIII in the A2 and C2 domains, the main targets of FVIII inhibitors. The rpFVIII concentrate is predicted to have an advantage over human-derived FVIII in CHA patients who have inhibitors since previous studies demonstrated that the antibodies have a median of only 15% cross-reactivity with plasma-derived porcine FVIII.[18]

Regulatory approval for rpFVIII for the treatment of bleeding episodes in adults with AHA was received for OBIZUR®; per the product label, the initial dose of OBIZUR® is 200 U/kg, with subsequent dosing dependent on the location and severity of bleeding episode, target factor VIII levels, and the patient's clinical condition.[17]

Influence of Anti-pFVIII Inhibitor Titer on the Loading Dose

Anti-pFVIII inhibitors are neutralizing antibodies against pFVIII that neutralize the pFVIII, and thereby reduce its hemostasis effect. Anti-pFVIII inhibitors can be quantified in plasma by the Bethesda assay, which measures the ability of the patient's plasma to neutralize exogenous pFVIII when incubated together.

The amount of pFVIII required to neutralize the anti-pFVIII activity is factored in. A BU is defined as the amount of anti-pFVIII inhibitor in a plasma sample which will neutralize 50% of 1 unit of pFVIII in normal plasma after 2 hour incubation at 37°C.

Only the inhibitor that is distributed in the plasma volume (PV) is initially available to neutralize the infused FVIII; PV is calculated using the following formula:

PV = Blood Volume x (1 – [hematocrit{Hct}%/100])

Normal blood volume is approximately 80 mL/kg for adults.

Therefore, PV = 80 x (1 – [Hct%/100]).

One BU of anti-pFVIII inhibitor will neutralize 50% of 1 unit of pFVIII; therefore, it is assumed that 0.5 U FVIII will be required for each 1 BU of inhibitor. The amount of BAX802 required to neutralize the anti-pFVIII activity can be estimated using the following:

Body weight x 80(1 - [Hct%/100]) x 0.5 x anti-pFVIII titer (BU) =
body weight x 40(1-[Hct%/100]) x anti-pFVIII titer (BU).

Proposed Dosing Regimen of BAX802 in Study BAX802 Surgery

This regimen for loading dose of BAX802 proposed for Study BAX802 Surgery takes into account the titer of anti-pFVIII inhibitors. This regimen for loading dose of BAX802 proposed for Study BAX802 Surgery takes into account the titer of anti-pFVIII inhibitors. The dosing scheme to be used in Study BAX802 Surgery is presented in Section 8.7.3.3.

The loading dose of BAX802 for a CHA subject with inhibitors undergoing major surgery is calculated using the following formula:

80 U/kg + body weight x 40(1-[Hct%/100]) x anti-pFVIII titer (BU)

For example, for a 70 kg subject undergoing major surgery and having hematocrit 45% and anti-pFVIII titer 3 BU, the loading dose of BAX802 will is calculated as follows:

80 (70) + 70 x 40(1-[45/100]) x 3 = 10,220 U

This dosing scheme should reasonably predict the loading dose before surgery that will provide sufficient FVIII levels needed for effective hemostasis.

Subsequent doses, dosing frequency, and duration of treatment will be based on clinical judgment and measured FVIII levels achieved, and will require empirically based adjustments until hemostasis is achieved (Table 5).

This dosing algorithm is essentially equivalent to that proposed by Kasper (2004) when using FVIII in the treatment of patients with low titer inhibitors.[19]

8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study will be approximately 20 months from study initiation (ie, first subject enrolled) to study completion (ie, last subject, last visit). The recruitment period is expected to be 13 to 16 months.

The duration of subject participation depends on the nature of the invasive procedure: it will run from the signing of the informed consent until completion of the End of Study Visit up to 6 weeks post-surgery (surgery = Day 0), unless prematurely discontinued. Study completion is defined by the End of Study Visit after discharge.

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

The primary outcome measure is the GHEA score (Table 1), which is composed of 3 individual ratings:

- Assessment of intraoperative hemostatic efficacy of BAX802 performed by the operating surgeon (see Table 2)
- Assessment of postoperative hemostatic efficacy of BAX802 at postoperative Day 1 (approximately 24 hours after surgery) performed by the operating surgeon (see Table 3)
- Assessment of postoperative hemostatic efficacy of BAX802 at Day 14, performed by the investigator (see Table 4)

The scores of each of the 3 individual ratings described above, will be added together to form a GHEA score according to Table 1. For a GHEA score of 7 to be rated "excellent" no individual assessment score should be less than 2 (i.e. one individual assessment score must be 3 and the other two individual assessment scores must be 2). The only other option to achieve a GHEA score of 7 is for two individual assessment scores of 3 and one individual assessment score of 1. Although this GHEA score will not qualify for a rating of "excellent," the GHEA score will satisfy the definition of "good," (with no individual assessment score less than 1). All possible combinations of the individual assessment scores and their related ratings are provided in Supplement Section 20.6. Missing scores will be counted as 0.

Table 1: Global Hemostatic Efficacy Assessment (GHEA)	
Assessment	**GHEA Score**
Excellent	7[a] to 9 (with no category scored < 2)
Good	5 to 7[a] (with no category scored < 1)
Fair	3 to 4 (with no category scored < 1)
None	0 to 2 (or at least one category scored 0)

[a] For a GHEA score of 7 to be rated "excellent" (with no individual assessment scores less than 2), at least 1 individual assessment score must be 3 and the other 2 individual assessment scores must be at least 2; otherwise a score of 7 is rated "good".

Table 2: Intraoperative Efficacy Assessment Scale		
A	*At the time of discharge from the OR, the operating surgeon will assess the intraoperative hemostatic efficacy*	
Rating	**Criteria**	**Score**
Excellent	Intraoperative blood loss was less than or equal to that expected for the type of procedure performed in a non-hemophilic population (≤ 100%)	3
Good	Intraoperative blood loss was up to 50% more than expected for the type of procedure performed in a non-hemophilic population (101 - 150%)	2
Fair	Intraoperative blood loss was more than 50% of that expected for the type of procedure performed in a non-hemophilic population (> 150%)	1
None	Uncontrolled hemorrhage that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy	0

Table 3: Postoperative Efficacy Assessment Scale (Postoperative Day 1)		
B	*On postoperative Day 1, the operating surgeon will assess the postoperative hemostatic efficacy by the operating surgeon*	
Rating	**Criteria**	**Score**
Excellent	Postoperative blood loss was less than or equal to (≤ 100%) that expected for the type of procedure performed in a non-hemophilic population	3
Good	Postoperative blood loss was up to 50% more (101% - 150%) than expected for the type of procedure performed in a non-hemophilic population	2
Fair	Postoperative blood loss was more than 50% (> 150%) of that expected for the type of procedure performed in a non-hemophilic population	1
None	Significant postoperative bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy	0

Table 4: Postoperative Efficacy Assessment Scale (Day 14)		
C	*At Day 14, a hematologist will assess the postoperative efficacy*	
Rating	**Criteria**	**Score**
Excellent	Postoperative blood loss was less than or equal to (≤ 100%) that expected for the type of procedure performed in a non-hemophilic population, Required blood components for transfusions were less than or similar to that expected in non-hemophilic population	3
Good	Postoperative blood loss was up to 50% more (101% - 150%) than expected for the type of procedure performed in a non-hemophilic population Required blood components for transfusions were less than or similar to that expected in non-hemophilic population	2
Fair	Postoperative blood loss was more than 50% of that expected for the type of procedure performed in a non-hemophilic population (> 150%) Required blood components transfusions were greater than that expected in non-hemophilic population	1
None	Significant postoperative bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy Required blood components for transfusions were substantially greater than that expected in non-hemophilic population	0

8.4.2 Secondary Outcome Measures

8.4.2.1 Efficacy

1. Intra- and postoperative blood loss compared to the estimated volume of expected average blood loss and expected maximum blood loss in a comparable healthy individual as predicted preoperatively by the investigator/surgeon at the following time points:
    - Intraoperative, at the end of surgery
    - Postoperative Day 1, approximately 24 hours after surgery
    - Postoperative Day 14
2. Daily and total weight-adjusted administration of BAX802 per subject
3. Volume of blood, red blood cells, platelets, and other blood products transfused
4. Occurrence of bleeding episodes during the intra- and postoperative periods and additional need for surgical intervention
5. Efficacy of the treatment of intercurrent, unrelated bleeding episodes in the postoperative period.

8.4.2.2 Safety

1. Development of, and changes to, the titer of inhibitory and binding antibodies to rpFVIII
2. Development of, and changes to, the titer of inhibitory and binding antibodies to hFVIII
3. Development of binding antibodies to BHK proteins
4. Occurrence of thrombotic events
5. Incidence of severe allergic reactions (eg, anaphylaxis)
6. Incidence of other IP-related AEs
7. Incidence of clinically significant changes in vital signs and routine laboratory parameters (hematology, clinical chemistry)

8.5 Randomization and Blinding

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

8.6 Study Stopping Rules

The study will be halted (enrollment stopped), pending further review by the internal Safety Monitoring Committee (iSMC) and sponsor, if one or more of the following criteria are met:

1. Two or more subjects develop a severe anaphylactoid reaction or any other serious adverse event (SAE) related to BAX802 that would not be expected with a currently licensed rpFVIII product (OBIZUR®)
2. Other AEs that are deemed to pose unacceptable risks to subjects.

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

1. The sponsor decides to terminate the study based upon iSMC recommendation or its own assessment of safety
2. The sponsor decides to terminate the study at any time for administrative reasons.

8.7 Investigational Product(s)

BAX802 will be supplied as white lyophilized powder in 3 mL glass vials containing nominally 500 units per vial for reconstitution with 1.0 mL sterile water for injection.

8.7.1 Packaging, Labeling, and Storage

BAX802 will be supplied in a lyophilized form. For specific instructions for reconstitution, please refer to the Study Manual. A sufficient quantity of BAX802 will be supplied to each study site, as well as an acknowledgement of receipt form.

The core label texts for all packaging units will be translated or adjusted, to be in compliance with applicable regulatory requirements, national laws in force and in accordance with the local languages. Minimally each vial will bear a label with the following information:

- Sponsor name
- Study number
- Pharmaceutical dosage form
- Route of administration
- Name of IMP and actual quantity of dose units
- Batch number
- Space on which to record the subject number
- The statement 'For clinical trial use only' or 'Caution: new drug limited by Federal Law to investigational use' or 'To be used only by a qualified investigator', as appropriate
- Name, address and telephone number of the Sponsor, Contract Research Organization (CRO) or investigator, if appropriate
- Storage conditions
- Expiry or manufacturing date, as appropriate

The investigator or designee will only dispense BAX802 to subjects included in this study.

8.7.2 Reconstitution and Administration

The reconstitution procedures for BAX802 are detailed in the Pharmacy Manual. Reconstituted BAX802 should be kept and administered at room temperature and must be administered within 3 hours of reconstitution.

BAX802 will be administered as an intravenous infusion per the dosing schema for major and minor surgeries (Table 5).

8.7.3 Description of Treatment

8.7.3.1 FVIII Maintenance Plan

Based on the category (minor or major) and type of surgery, the investigator must outline the expected FVIII maintenance plan with target peak and trough levels covering the surgical, dental or invasive procedure until expected wound healing. The FVIII maintenance plan will be provided to the medical director/designee to ensure that the recommendations regarding FVIII target levels as provided in the protocol are followed. Each FVIII maintenance plan for major surgeries requires prior approval of the medical director. The FVIII levels measured intra/postoperatively will be compared with the FVIII maintenance plan. Slight deviations from the predefined substitution plan are allowed based on investigators clinical judgment and available laboratory FVIII data.

8.7.3.2 Perioperative Dosing

Adjustments to the dose and frequency of BAX802 dosing during the intra- and postoperative period should follow the maintenance plan provided by the investigator prior to surgery. Adjustments must be based on regular FVIII activity measurements determined at pre- and post-dosing of BAX802 and will depend on the type of the surgery performed and the intensity of the hemostatic challenge.

8.7.3.3 Dosing Schedule and Requirements

8.7.3.3.1 General

The dose and frequency of BAX802 administered will be individualized based on the subject's PK parameters for major surgeries and the most recent IR value for minor surgeries and the required FVIII target levels.

As described in Section 8.2.2, the loading dose will be calculated according to the following formula:

Loading Dose of BAX802:

- Major Surgery: 80 U/kg + body weight (kg) x 40(1-[Hct%/100]) x anti-pFVIII titer (BU), administered approximately 1 hour prior to the surgery
- Minor Surgery: 50 U/kg + body weight (kg) x 40(1-[Hct%/100]) x anti-pFVIII titer (BU), administered approximately 1 hour prior to the surgery

The loading dose of BAX802 for a CHA subject with inhibitors undergoing major surgery is calculated using the following formula:

80 U/kg + body weight (kg) x 40(1-[Hct%/100]) x anti-pFVIII titer (BU)

For example, for a 70 kg subject undergoing major surgery and having hematocrit 45% and anti-pFVIII titer 3 BU, the loading dose of BAX802 will be calculated as follows:

$$80\ (70) + 70 \times 40(1-[45/100]) \times 3 = 10{,}220\ \text{U}$$

Subsequent doses, dosing frequency, and duration of treatment will be based on the clinical judgment and measured FVIII levels achieved, and will require empirically based adjustments until hemostasis is achieved based on the following calculation (Table 5):

Required dose (IU) =
[body weight (kg) x desired FVIII rise (IU/dL or % of normal)]/1.2 (IU/kg per IU/dL).

Table 5: Dosing for Perioperative Management

Type of Surgery	Factor VIII Level Required (% of normal or IU/dL)	Loading Dose	Subsequent Dose
Major (see Section 8.2.1.1)	**Prior to surgery:** ≥ 80% **Postoperative up to 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)	80 U/kg + body weight (kg) x 40(1-[Hct%/100]) x anti-pFVIII titer (BU)[1], administered approximately 1 hour prior to the surgery	Titrate subsequent doses to maintain recommended FVIII trough levels and individual clinical response using following formula: Required dose (IU) = [body weight (kg) x desired FVIII rise (IU/dL or % of normal)]/1.2 (IU/kg per IU/dL)
Minor (see Section 8.2.1.2)	**Prior to surgery:** ≥ 50% **Postoperative up to 72 hours (Day 1- Day 3):** ≥ 50% **Postoperative Day 4 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)	50 U/kg + body weight (kg) x 40(1-[Hct%/100]) x anti-pFVIII titer (BU)[1], administered approximately 1 hour prior to the surgery	

[1] pFVIII titer and hematocrit information available from screening lab result will be used.
Note: Plasma levels of FVIII should not exceed 200% of normal or 200 units per dL.

If at any time during the study, a subject does not respond to BAX802 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. In the event of unexplained, excessive bleeding, the subject will be treated by whatever means necessary until adequate hemostasis is achieved. If other rescue medications become necessary, the subject will subsequently be withdrawn from this BAX802 surgery study. Adverse events and the details of concomitant medication and blood product use coincident with the treatment of all unanticipated bleeding will be recorded. The use of adjunct antifibrinolytic therapy (such as tranexamic acid) is allowed if clinically indicated by the investigator and/or according to the standard of care of the subject's institution.

8.7.3.3.2 Preoperative and Loading Dose

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

The initial loading dose will be administered within 60 minutes prior to surgery (prior to incision/intubation).

In case of major surgery, FVIII target levels should be ≥ 80% of normal, in case of minor surgery FVIII levels should be at ≥ 50%.

The surgery may only start after FVIII levels are in the target levels.

ALL subsequent dosing of BAX802 should be preceded by measurement of residual FVIII levels and dose adjustments must be based on the most recent residual FVIII activity levels.

Note: Plasma levels of FVIII should not exceed 200% of normal or 200 units per dL.

Note: Dose adjustments based on aPTT values are not allowed.

8.7.3.3.3 Postoperative Dosing

Major Surgery

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

Note:

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

ALL subsequent dosing of BAX802 must be preceded by measurement of residual FVIII levels and the dose adjusted as needed. Dosing adjustments based on aPTT values are not allowed.

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

Beginning on postoperative Day 1 (ie, the day following the day of surgery) through discharge, subjects will have a BAX802 pre-dosing (within 30 minutes) and after 15 ±5 minutes a post-dosing FVIII level measurement at least once per day in order to assess the adequacy of BAX802 therapy during the postoperative period. For consistency, it is recommended that the daily blood draws are performed at the same time of the day, such as morning blood draws.

8.7.3.3.4 Dosing for Unrelated Bleeding Episodes During the Postoperative Period

Unrelated bleeding episode is defined in Section 11.2.5.

The BAX802 dosing regimen for treatment of these bleeding episodes will be based on the guidelines in Table 6. These guidelines may be adjusted by the investigator based upon his or her clinical judgment.

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

Repeat infusions of BAX802 can be administered to treat these bleeding episodes, as per investigator's discretion.

When bleeding is controlled, additional infusions of BAX802 to maintain hemostasis are permitted, if required. Infusions given to maintain hemostasis should be documented in the eCRF.

For a detailed description of bleeding episodes into different sites see Supplement 20.7.

Table 6: BAX802 Treatment Guidelines for Unrelated Bleeding Episodes			
Type of Bleeding Episode	**FVIII Level Required (%)**	**Loading Dose**	**Subsequent Dose**
Minor Early hemarthrosis, mild muscle bleeding, or mild oral bleeding, including, epistaxis	20% to 40%	Loading dose (IU) = [body weight (kg) x desired FVIII rise (IU/dL or % of normal)]/1.5 (IU/kg per IU/dL) + body weight (kg) x 40(1-[Hct%/100]) x anti-pFVIII titer (BU) [1, 2]	Titrate subsequent doses to maintain recommended FVIII trough levels and individual clinical response using following formula: Required dose (IU) = [body weight (kg) x desired FVIII rise (IU/dL or % of normal)]/1.5 (IU/kg per IU/dL)
Moderate Moderate bleeding into muscles, bleeding into the oral cavity, definite hemarthrosis, and known trauma	30% to 60%		
Major Significant gastrointestinal bleeding, intracranial, intra-abdominal, or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces or iliopsoas sheath, fractures, head trauma	60% to 100%		

[1] pFVIII titer and hematocrit information available from Day 14 laboratory results (if available) will be used. If Day 14 laboratory results are not available, Screening laboratory results shall be used to make dosing calculations rather than waiting for Day 14 results.
[2] BAX802 will not be used to treat these bleeding episodes if the Day 14 anti-pFVIII titer (if available) is > 10 BU.
Note: Plasma levels of FVIII should not exceed 200% of normal or 200 units per dL.

8.7.4 Thrombosis Prophylaxis and Topical Hemostatics

Commercially available gelatin sponges, topical thrombin, fibrin sealants, absorbable collagen preparations or anti-fibrinolytics (eg, tranexamic acid, ε-amino caproic acid) may be used according to each institution's standard of care. Details, including the dose, of all adjunctive hemostatic medication used will be recorded in the eCRFs designed for this study and the reason for use given.

Thrombosis prophylaxis can be administered at the discretion of the investigator according to the standard of care of each institution and recorded into the respective eCRF. Thrombosis prophylaxis should preferably consist of mechanical measures such as intermittent pneumatic compression (IPC), compression stockings and early mobilization.

Pharmacologic thrombosis prophylaxis such as low molecular weight heparin (LMWH) may be considered for certain surgical interventions such as major orthopedic surgery after careful evaluation by the investigator of the potential risks and benefits.

8.7.5 Investigational Product Accountability

The investigator will ensure that the IP(s) 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(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. IP(s) must be dispensed only at the study site or other suitable location (eg, infusion center; home, as applicable per study design). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) 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(s) 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, 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.

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 ≥ 18 to ≤ 65 years old at the time of screening
2. Subject has provided signed informed consent
3. Subject has severe (FVIII level < 1%) or moderately severe (FVIII level ≤ 2%) CHA with inhibitors to human FVIII, as tested at screening at the central laboratory
4. Subject requires elective surgery or other invasive procedures
5. Subject is not currently receiving ITI therapy
6. Subject has a Karnofsky performance score of ≥ 60
7. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm3 at screening
8. Subject is hepatitis C virus negative (HCV-) by antibody or polymerase chain reaction (PCR) testing; or HCV+ with chronic stable hepatitis disease
9. Subject is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

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

1. The subject requires emergency surgery
2. The subject's weight is < 35 kg or > 120 kg
3. Clinically symptomatic liver disease (eg, ≥ 5 X upper limit of normal alanine aminotransferase [ALT], as confirmed by central laboratory at screening, clinical evidence of portal hypertension, severe hypoalbuminemia or a documented prothrombin time/international normalized ratio (PT/INR) > 1.5)
4. Clinically symptomatic renal disease (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening
5. Anti-porcine inhibitor > 10 BU prior to surgery
6. Platelet count < 100,000/µl
7. Active condition of coagulation disorder such as von Willebrand disease

8. Planned use of α-interferon with or without ribavarin for HCV infected patients or planned use of a protease inhibitor for HIV infected patients. Patients currently taking any of these medications for ≥ 30 days are eligible
9. Known hypersensitivity to rpFVIII, or hamster or murine proteins
10. Subject has been exposed to an IP 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
11. Unable to tolerate quantity of blood to be drawn for protocol procedures
12. Subject is a family member or employee of the investigator.

9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (ie, reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) are described in Section 10.7, Section 20.3, and Section 20.4.

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

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

- AEs/SAEs that in the investigator or sponsor opinion, poses an unacceptable risk for continued dosing in the subject
- The subject is determined by the sponsor or investigator to be noncompliant with administration of IP, despite evidence of retraining of the subject. The subject will be discontinued from further participation in the study
- Participation in another clinical study involving an IP during the course of the study
- The subject experiences a severe anaphylactic reaction
- The subject had uncontrolled hemorrhage that was the result of inadequate therapeutic response despite proper dosing of rpFVIII, necessitating rescue therapy with bypassing agents.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient 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 (241502) to be provided by the sponsor, 2-digit number study site number (eg, 02) 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 02 will be identified as Subject 241502-02003. All study documents (eg, CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (eg, collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

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

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

Subjects who fail screening due to a single laboratory test result that does not meet eligibility criteria may have that laboratory test repeated at the discretion of the investigator. This will include a repeat of only the failed assessment; complete re-screening will not be necessary. In these cases, a new SIC is not required; the subject will maintain their original SIC. The repeat of a screening assessment is allowed once. A repeat assessment must take place within 42 days of the initial screening for any subject requiring repeat of a screening assessment. If this timeframe is exceeded, then all screening assessments must be repeated and the subject assigned a new SIC. Exemptions are possible for administrative reasons and have to be approved by the sponsor. Subjects with an inadequate interval between screening and prior IP drug (other than BAX802) administration or prior participation in a drug or device study (ie, 30 days), may be re-screened only once and only when the required interval is reached.

The screening assessment should be performed within 45 days prior to the planned elective surgery.

The overall study design is illustrated in Supplement Figure 1. Details on the procedures to be performed at each study visit, including screening, can be found in Supplement 20.3 and Supplement 20.4.

10.4 Study Periods

The study will be divided into 5 periods:

1. Screening
2. Preoperative
3. Intraoperative
4. Postoperative
5. End of study

A detailed description of study procedures per study period is provided in Supplement 20.1.

10.4.1 Discharge/End of Study Visit

Discharge Visit will be performed when the subject is discharged and the End of Study Visit will be performed 42 to 49 days following the completion of the surgical procedure. In cases where the Discharge Visit would occur within 3 days of either the Day 14 or the End of Study visit, the respective visits will be done as a single visit.

10.4.2 Unscheduled Visits for Unrelated Bleeding Episodes

If the unrelated bleeding episode occurs after subject's discharge, subject will visit the investigator (Table 11). If these unrelated bleeding episodes occur during the subject's stay in hospital, subjects will be treated with BAX802. If these unrelated bleeding episodes occur after the subject has been discharged, subjects will be treated with BAX802 or with standard of care, as per investigator's discretion. Follow up visits will be performed as per Table 11.

10.5 Medications and Non-Drug Therapies

The following medications are **not** permitted:

Medications:

- Hemophilia inhibitor bypassing therapy (recombinant factor VIIa [NovoSeven] within 3 hours or aPCC [FEIBA)] within 6 hours prior to initial BAX802 administration) unless used as a rescue medication (Section 10.5) after failure/study withdrawal
- Hemophilia medication other than BAX802 at any time during the study.

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

The following medications and non-drug therapies are permitted within 30 days before study entry and during the course of the study:

Medications:

- The management of a serious thrombo-embolic event may require anticoagulant medication and this may need to be administered concurrent with the use of BAX802 to ensure that a re-bleed or continuing severe hemorrhage does not occur on withdrawal of BAX802 (see Section 10.6). In such instances the Sponsor's medical monitor should be consulted.
- Any medications deemed necessary by the subject's physician to treat or prevent any medical condition (with the exception of those listed as not permitted)
- Any over-the-counter medication used by the subject to treat symptoms or signs of any medical condition
- Supplemental vitamins, minerals

Non-drug therapies:

- Any non-drug therapy (eg, physiotherapy) deemed necessary by the subject's physician to treat or prevent any medical condition

10.6 Rescue Medications

Bypassing agents (FEIBA or NovoSeven) can be used as a rescue medication if expected plasma FVIII activity levels are not attained or if bleeding is not controlled despite proper dosing of BAX802 during the intra- or postoperative period of the study. At least 2 doses of BAX802 needs to be administered before the subject is considered to be a treatment failure and switched to the rescue medication.

10.7 Subject Completion/Discontinuation

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

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation 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), 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 20.3 and Supplement 20.4.

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.

10.8 Procedures for Monitoring Subject Compliance

Subject compliance with the procedures and treatment(s) outlined above will be monitored by direct review of the subject's source data at the sites and evaluated against the protocol requirements. Additionally, electronic edit checks will be performed on all protocol-specified procedures and treatment data that are collected to ensure quality and accuracy. Deviations from the protocol-specified procedures and treatments will be noted in the final study report.

All study procedures are to be performed under the direct supervision of the investigator/a licensed healthcare professional at the study site, and thus, no separate procedures will be used to monitor subject compliance.

11. ASSESSMENT OF EFFICACY

11.1 Primary Efficacy Endpoint: Global Hemostatic Efficacy Assessment Score

The primary outcome measure is the GHEA, which is composed of 3 individual categorical ratings which will be added together to form a GHEA score according to Table 1 (see Section 8.4.1).

11.2 Secondary Efficacy Endpoints

11.2.1 Blood Loss

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

Prior to the surgery, the surgeon/investigator will predict the estimated volume (in 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 end of study visit).

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

11.2.2 Blood Transfusions

The type and volume (in mL) of blood products will be recorded from initiation of the intervention to postoperative Day 14. Furthermore, also salvage of blood obtained from autologous transfusion systems, eg, cell savers, will be recorded. In addition, the type and volume of fluid replacement and volume expanders will be recorded as concomitant medication (eg, volume of salvaged blood, red blood cells, platelets and other blood products transfused)

11.2.3 Bleeding Episodes

Any clinically relevant bleeding episodes (as assessed by the investigator), as well as the need for any further surgical interventions, will be recorded. Study subjects will be closely monitored for the occurrence of bleeding episodes during the entire intra- and postoperative period, until the time of discharge or until the subject resumes his previous treatment regimen, whichever is later.

Any subject who is deemed to have excessive, unexplained bleeding will have blood drawn for measurement of FVIII levels. Treatment of such events should be performed as per standard of care at the institution.

11.2.4 BAX802 Administration

The daily and total weight-adjusted administration of BAX802 per subject will be recorded.

11.2.5 Hemostatic Efficacy Rating for Treatment of Inter-current, Unrelated Bleeding Episodes

An intercurrent, unrelated bleeding episode is defined as any bleeding occurring at a different anatomical site than the surgery site during the postoperative period. If these unrelated bleeding episodes occur during the subject's stay in hospital, subjects will be treated with BAX802 (Note: BAX802 will not be used to treat these bleeding episodes if the Day 14 anti-pFVIII titer [if available] is > 10 BU). If these unrelated bleeding episodes occur after the subject has been discharged, subjects will be treated with BAX802 or with standard of care, as per investigator's discretion. The dosing regimen is provided in Table 6.

If subject is treated with BAX802 for unrelated bleeding episodes, the subject will rate the severity (minor, moderate, or major) of the bleeding episode and will rate the overall treatment response at 24 ±2 hours after the initiation of treatment and at the resolution of bleed (if not resolved within 24 hours) using a 4-point efficacy rating scale (Table 7). 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 5, multiple infusions of BAX802 may be administered for the treatment of a bleeding episode. The overall response to all infusions combined is the rating that will be recorded at resolution of bleed.

Table 7: Efficacy Rating Scale for Treatment of Bleeding Episodes	
Excellent	Full relief of pain and/or 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.

11.3 Factor VIII Activity

Blood will be obtained for assessment of FVIII activity at screening (tests to be performed at the **central laboratory**). Results from **local laboratory** will be used to make any dosing decisions.

Blood will be obtained for assessment of FVIII activity for patient management purposes at the following timepoints (tests to be performed at the **local laboratory**, with additional back-up samples to be tested in one batch at the **central laboratory**):

- Within 60 minutes prior to the administration of the initial loading dose preoperatively and 15 ±5 minutes post-infusion. If a rebolus with BAX802 is required to obtain the required FVIII levels, an additional blood sample needs to be drawn 15 ±5 minutes following the rebolus with BAX802.
- Postoperatively until day of discharge from the investigative site: daily within 30 minutes prior to the infusion of BAX802 and 15 ±5 minutes post-infusion. Pre- and post-dosing blood draws for FVIII activity level determination should also be performed for each BAX802 administration.
- FVIII activity will also be assessed if the subject has excessive, unexplained bleeding at any time intra-or postoperatively, or whenever deemed necessary according to the institution's standard of care.

11.3.1 Blood Sampling and Processing for FVIII Analysis

At each blood sampling time point whole blood will be collected in blood sampling tubes will be collected in S-Monovette® tubes (Sarstedt, Nümbrecht, Germany) containing 3.2% trisodium citrate, or equivalent blood drawing equipment (eg, Vacutainer tubes), and immediately mixed. The citrated whole blood samples will be capped and transported at room temperature (ie, 20 - 25°C) to the local clinical laboratory for centrifugation, processing, and storage. Monovettes must be kept in an upright position at all times to avoid leakage.

All samples taken through 6 hours post-dosing will be collected from an extremity other than that used for the infusion of study product. Thereafter, either extremity may be used to obtain samples.

If the subject has a central 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 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 sample.

All citrated plasma samples will be stored and shipped to the central laboratory at ≤ -70°C for testing.

All back-up samples collected during the perioperative period will be shipped to the central laboratory as soon as possible in one batch and analyzed, as needed.

Blood samples will be analyzed for FVIII activity (1-stage clotting assay and the chromogenic assay) at the central laboratory. The 1-stage FVIII activity assay will serve as the primary assay; the chromogenic assay of FVIII activity will be used to provide supportive data. Local laboratories are expected to use whichever FVIII assay is available (1-stage clotting assay or the chromogenic assay).

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

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

12.1.1.1 Serious Adverse Event

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

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

- Thromboembolic events (eg, stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism)

Planned hospitalization for any study procedures as per the protocol will not be considered as 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.

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 are collected under other study endpoints and thus are not reportable on the AE CRF, nor will they be included in the analysis of AEs:

Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be assessed as part of the efficacy assessments. However, the investigator may decide that the event is an AE if the event also would have occurred in a normal patient under the same circumstances. If a bleeding episode was caused by an injury, the injury will be reported as an AE.

All other/Each AE from the first IP exposure until study completion or 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 resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (ie, the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

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

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the provided SAE Report 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, 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.

12.1.2.3 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Table 9) and Section 12.1.

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

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the IP, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported via the Electronic Data Capture (EDC) system by completing the relevant electronic Case Report Form (eCRF) page(s) in English. Once the SAE has been recorded in the EDC system, the Sponsor and other designated recipients will be informed of the event automatically. For instances in which the EDC may become unavailable, SAEs must be reported using the back-up paper SAE Report Form to meet the 24 hour timeline requirement (contacts and instructions to be provided in separate documentation). Once the EDC becomes available, the site must enter all SAE data as reported on the back-up paper SAE report form on the applicable eCRF pages.

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

- Protocol Number

- Subject identification number and demographics (gender, age at onset of event and/or date of birth)
- IP exposure
- Medical Term for Event (Diagnosis preferably)
- Description of the (S)AE, including:
  - Date of onset
  - (S)AE treatment (drug, dose, route of administration)
  - Causal relationship by the Investigator
  - Measures taken (ie, action taken regarding IP in direct relationship to the AE)
- Seriousness criteria (ie, death, life-threatening, or other criterion)
- Cause of death
- Autopsy findings (if available)
- Name, address, fax number, email, and telephone number of the reporting
- Investigator (for paper SAE Report Forms)

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 AE CRF (and SAE Report Form if eCRF is not available). These events will not be considered as SAEs and will not be included in the analysis of SAEs.

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

- Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be assessed as part of the efficacy assessments. If a bleeding episode was caused by an injury, the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (eg, abrasion of skin). Therefore, any hemophilia-related event (eg, hemarthrosis [presenting as swelling, pain, and decreased range of motion], bruising, hemorrhages, or pain at bleeding episode site) will not be reported as AEs. However, the Investigator may decide that the event is an AE if the event also would have occurred in a normal patient under the same circumstances.

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.

Medical history will include the collection of hemophilia history, bleeding episode history, and history of aPCC or rFVIIA usage for 12 months prior to screening. Relevant medical and surgical history and all medications taken 3 months prior to screening will also be collected.

All medications taken and non-drug therapies received within 3 months before enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Table 9), 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

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

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) and platelet counts.

Clinical chemistry and hematology assessments will be performed on EDTA-anticoagulated serum and whole blood, respectively, at the central laboratory. The frequency of blood draws for clinical and hematology assessments is provided in Table 10.

Details of blood sampling volumes are presented in the laboratory manual and master ICF.

12.7.1 Hematology, Clinical Chemistry, and Urinalysis

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) and platelet counts.

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

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening/baseline, all study visits (ie, pre- and perioperatively and daily while the patient is at the study site), and at study completion/termination. Hematology and clinical chemistry assessments will be performed on EDTA-anticoagulated whole blood and serum, respectively, at the central or local laboratory.

The urinalysis panel will consist of pH, protein, ketones, glucose, bilirubin, blood, urobilinogen, specific gravity by dipstick and microscopy if any findings are abnormal.

Urine will be obtained for assessment of urinalysis parameters at screening and at study completion/termination.

12.7.2 Viral Serology

Viral serology testing will include HIV-1 and HIV-2 antibody, HAV antibody, HBV antibody, hepatitis B surface antigen (HBsAg), HCV antibody, and parvovirus B19 (immunoglobulin M [IgM] and immunoglobulin G [IgG] antibodies). The HCV titer will be confirmed by PCR for all subjects reported as HCV positive. All viral serology assessments will be performed at screening. Any positive test will be repeated using a new blood sample.

12.7.3 Immunogenicity

Immunogenicity assessments will include anti-pFVIII and hFVIII binding and inhibitory and anti-BHK binding antibodies.

Blood samples will be collected for the assay of anti-pFVIII and hFVIII binding and inhibitory antibodies and anti-BHK binding antibodies at the times indicated in Table 9 and Table 10.

All FVIII and BAX802 inhibitor assays related to study subject management decisions by the investigator will be performed at the investigator's local laboratory. Local laboratories will be pre-qualified for ability to provide these services prior to study participation. Further details for laboratory pre-qualification will be provided separately by the sponsor.

A central reference laboratory will perform assays (anti-pFVIII, anti-hFVIII, and anti-BHK) on samples taken at the Screening, Day 14, and End of Study Visits.

Binding antibodies to pFVIII, hFVIII, and BHK, will be measured using ELISA. The assessment of inhibitory antibodies to porcine and hFVIII will be determined using a Bethesda assay (with the Nijmegen modification if possible). Further details on blood collection, tube preparation and shipment will be provided in the Study Manual.

12.7.4 Assessment of Laboratory Values

12.7.4.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each laboratory value will be recorded on the CRF. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes an 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.

12.7.5 Biobanking

Back up 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.

Samples are planned to be obtained at the following time points: Screening, Presurgery, Postoperative, Discharge, End of Study/Termination, and will be stored appropriately. This will ensure that there is sufficient material should any results require a re-test or additional testing (eg, further evaluation of an abnormal test or an AE).

Additional back up citrated plasma samples will be taken at each PK blood sampling time point to ensure if re-testing is required as well as possible additional assays for quality checks to comply with EMEA requirements there will be sufficient samples.

Backup samples that remain after study testing is done may be stored and used for additional testing of FVIII activity or safety parameters (eg, further evaluation of an abnormal test or an AE). Samples will be stored in a coded form for no more than 2 years after final study report completion 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) measured once at screening, and weight (lb or kg) will also be collected.

Vital signs will be measured at screening and within 30 minutes before and 15 ±5 minutes after administration of IP, at each study visit, and at study completion/termination. 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.

12.9 Karnofsky Performance Test

The Karnofsky Performance Test is a status scale (0 - 100) utilized to measure the level of activity and medical care requirements in subjects. It is an investigator based assessment of patient status which evaluates the subjects' ability to carry on normal life activities, as well as the symptoms of their disease.[20] Subjects will be scored using this scale at screening.

12.10 Special Treatment Considerations

Patients will be screened for eligibility in the study as described in the inclusion/exclusion criteria (Section 9.1 and Section 9.2), and will be informed of the study specific restrictions and requirements of the study. Patients who are not willing to comply with the study requirements and restrictions of the study will not be eligible for enrollment.

All biological agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include, but are not limited to:

- skin rash
- pruritus (itching)
- urticaria (hives)
- angioedema (for example, swelling of the lips and/or tongue)
- anaphylactic reaction.

Proteins may also cause redness, itching, swelling, or pain locally at the infusion site.

Sometimes, these reactions can be life-threatening. Therefore, all patients should be closely monitored for signs or symptoms that could result from such reactions, educated on the signs or symptoms of these types of reactions, and instructed to contact the study site immediately if any of the symptoms are experienced following an injection. If a patient experiences an acute allergic/hypersensitivity reaction after an injection of investigational product, he or she should be managed appropriately and given instruction to receive relevant supportive care. Additionally, for an event judged by the investigator to be a potential systemic allergic/hypersensitivity reaction, a blood sample should be drawn to test for anti-drug antibodies.

Patients who experience a potentially severe allergic reaction will be discontinued from study drug, they will complete a Termination/Study Completion Visit, and will be monitored for stabilization, or resolution of the AE. Premedications to prevent allergic reactions will not be permitted as severe allergic reactions are an outcome measure for this study.

13. STATISTICS

Data handling will be the responsibility of the contract research organization (CRO). The data will be inspected for inconsistencies by performing validation checks.

All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the statistical analysis plan (SAP) prepared by the CRO and approved by the sponsor before database lock.

13.1 Sample Size and Power Calculations

The sample size of at least 10 evaluable male subjects, 5 of which must have major surgery as defined in the protocol, was chosen to provide sufficient evidence of safety and effectiveness for this indication and is not based on statistical considerations.

13.2 Datasets and Analysis Cohorts

Classification into the analysis sets will be conducted prior to the database lock.

13.2.1 Safety Analysis Set

The safety analysis set (SAS) will be comprised of all subjects who received any amount of BAX802.

13.2.2 Efficacy Datasets

13.2.2.1 Full Analysis Set

The full analysis set (FAS) will comprised of all subjects with at least one available hemostatic assessment.

13.2.2.2 Per-Protocol Analysis Set

The per-protocol analysis set (PP) will comprise all subjects with available perioperative hemostatic efficacy assessed by:

i) the operating surgeon within 60 minutes post-surgery

ii) postoperative hemostatic control assessed by the operating surgeon postoperatively at 24 hours, and

iii) postoperative hemostatic control assessed by the investigator during Day 14.

Only subjects who met all study entry criteria and who had no major protocol violations that might impact hemostatic efficacy assessments will be included in the PP analysis set.

13.3 Handling of Missing, Unused, and Spurious Data

All data will be evaluated as observed; no imputation method for missing values will be used. A subject who withdraws prior to the last planned observation in a trial period will be included in the analyses up to the time of withdrawal.

13.4 Methods of Analysis

For qualitative parameters, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of parameters will be presented. Quantitative parameters will be summarized by the population size (N for sample size and n for available data), mean, standard deviation, median, minimum, and maximum values.

13.4.1 Primary Outcome Measure

The primary efficacy measure will be the overall assessment of hemostatic efficacy assessed intraoperatively by the surgeon and postoperatively by the investigator (hemophilia physician) at postoperative Day 1 (ie, the day following the day of surgery) and at postoperative Day 14 visit, and will be summarized by the GHEA score and rated "excellent", "good", "moderate" and "none".

A treatment success will be defined as a rating of excellent and/or good.

Point estimates and corresponding two-sided exact confidence intervals (CIs) at the 90% confidence level will be calculated for the rate of hemostatic efficacy assessments with excellent/good outcome.

The primary efficacy analysis will be based on the FAS. As a supportive analysis, the same calculations will also be carried out on the PP population.

13.4.2 Secondary Outcome Measures

13.4.2.1 Secondary Hemostatic Efficacy Analysis

Descriptive statistics will be used to summarize the actual blood loss and transfusion requirements, respectively.

The summary of average daily and total weight-adjusted doses (average through postoperative Day 14) of BAX802 per subject as well as the occurrence of bleeding episodes will be provided using descriptive statistics.

For intercurrent, unrelated bleeding episodes in the postoperative period, descriptive statistics will be used to summarize the overall hemostatic efficacy rating at 24 ±2 hours after initiation of treatment and at resolution of bleed (if not resolved within 24 hours).

The secondary efficacy analysis will be performed on the FAS only.

13.4.2.2 Safety Analysis

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by presenting the number and percentage of subjects having any AE, having an AE in each system organ class, and having each individual AE as reported by preferred term. In the summaries, AEs will be counted only once per patient. If a patient reports the same AE more than once, it will be counted with its worst severity and closest relationship to the study product.

The number of subjects who experienced SAEs and the number of SAEs will be tabulated. In addition, the number of subjects who experienced AEs related to IP and the number of IP-related AEs will be tabulated and subcategorized for thrombotic events, inhibitory and total binding antibodies to rpFVIII and hFVIII, and binding antibodies to BHK proteins.

A listing of all AEs will be presented by subject identifier, age, preferred term, and reported term of the AE, duration, severity, seriousness, action taken, outcome, causality assessment, onset date, stop date, and medication or non-drug therapy to treat the AE. An overview table for AEs will be provided, presenting the number of AEs, the number of subjects with AEs and the corresponding percent of subjects in total, and by seriousness and relationship to study treatment. An additional summary table will present the total number of (mild, moderate, severe) AEs by system organ class and preferred term with relationship to IP.

Summary statistics over time will be presented for the continuous laboratory parameters. Descriptive statistics of changes from baseline (Day 0 - prior to surgery) by study visits will also be presented.

A frequency table of results of categorical laboratory parameters will be produced. Furthermore, laboratory abnormalities will be analyzed by shift tables where each subject will be counted only once with the worst grade in the summary tables.

All laboratory data will be listed with abnormal values.

Vital signs assessments as well as the corresponding changes from baseline will be summarized descriptively at each scheduled assessment.

The safety analysis will be based on the SAS.

13.5 Planned Interim Analysis of the Study

Interim analyses may be conducted, as needed, for this study.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

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

15.1.1 Investigator Report and Final Clinical Study Report

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

15.2 Training

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

15.3 Monitoring

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

15.4 Auditing

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

15.5 Non-Compliance with the Protocol

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

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

15.6 Laboratory and Reader Standardization

Not applicable; a central laboratory/reader will be used for all clinical assessments. Local laboratories are requested to provide their laboratory specifications for each assay used.

16. ETHICS

16.1 Subject Privacy

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

16.2 Ethics Committee and Regulatory Authorities

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

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

16.3 Informed Consent

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

All patients and/or their legally authorized representative must sign an ICF 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 ICF will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The ICF 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 ICF, 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 ICF will be updated, if necessary. This new information and/or revised informed consent form that has 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 Internal Safety Monitoring Committee

This study will be monitored by an internal Safety Monitoring Committee (iSMC). The iSMC will be comprised of Baxalta individuals with pertinent expertise that will review accumulating data from this study on a regular basis. For this study, the iSMC will be composed of individuals from Drug Safety/Pharmacovigilance, Clinical Research, Clinical Development, Data Management, and Biostatistics, who are not actively involved in this study. The iSMC will provide recommendations based on the available data. Details regarding iSMC are provided in the Safety Review Plan.

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. 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 Procedures per Study Period

Table 8: Flow Diagram of Required Procedures for Baxalta Clinical Study 241502

1. Screening

Written Informed Consent must be obtained prior to any study-related procedures

Screening activities should be performed within 45 days prior to the planned elective surgery.

The following screening procedures are required:

- Eligibility evaluation (review of inclusion/exclusion criteria)
- Hemophilia history, bleeding episode history, history of aPCC or rFVIIA usage for a year prior to screening
- Relevant medical and surgical history and all medications taken 3 months prior to screening
- Review of concomitant medications/non-drug therapies
- Complete physical examination (see Section 12.6)
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measure body weight and height; see Section 12.8)
- Karnofskys performance test assessment (see Section 12.9)
- Clinical laboratory assessments (see Table 10).

Table 8: Flow Diagram of Required Procedures for Baxalta Clinical Study 241502

2. Preoperative Procedures (Day 0)

Subjects will return to the study site prior to their scheduled surgery as instructed by site staff. Subjects will undergo the following procedures:

Prior to surgery

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

- Accurate prediction of volume of expected blood loss intraoperatively (from completion of the procedure until approximately 24 hours post-surgery) and for the overall perioperative time period (up to discharge/end of study [EOS])

Loading Dose and Post Dosing Laboratory Assessment

Within 60 minutes before initiating surgery, the subject will receive a loading dose of BAX802 to raise the plasma level of FVIII to ≥ 80% for major and to ≥ 50% for minor surgical, dental and invasive procedures.

Subjects will undergo the following procedures:

- **Prior to BAX802 loading dose:**
  - Record AEs, concomitant medication and non-drug therapy use
  - Physical examination, vital signs (pulse, respiratory rate, blood pressure and temperature) and weight
  - Laboratory Assessments including:
    - Hematology (without differential but including platelets)
    - Clinical chemistry
    - Within 15 - 30 minutes before loading dose, blood draw for:
      - FVIII activity
- **BAX802 loading dose:**
  - Loading dose of BAX802 to raise the plasma level of FVIII to ≥ 80% of normal for major and to ≥ 50% for minor surgical, dental and invasive procedures. It will be administered within 60 minutes prior to surgery (prior to incision/intubation).
- **After BAX802 loading dose:**
  - Laboratory assessment of FVIII activity: 15 ±5 minutes after infusion of the loading dose
  - Vital signs (pulse, respiratory rate, blood pressure and temperature) will be recorded 15 - 30 minutes after infusion
  - Confirmation that FVIII is adequate just prior to intubation/incision. Administration of additional dose of BAX802, if required. If another dose of BAX802 is necessary, an additional post-infusion FVIII activity determination must be performed 15 ±5 minutes following the infusion.
  - All samples taken through 6 hours post-infusion will be collected from an extremity other than that used for the infusion of study product. Thereafter, either extremity may be used to obtain samples.

The surgery can begin only if FVIII is in target range (Table 5).

Throughout: Monitoring of AEs and concomitant medication and non-drug therapy use.

Table 8: Flow Diagram of Required Procedures for Baxalta Clinical Study 241502

3. Intraoperative Procedures (Day 0)

During the surgical procedure:

- Record AEs and concomitant medication and non-drug therapy use
- Record blood product usage, including salvaged blood, packed red blood cells (pRBC), platelets, and other blood products.
- Administer additional BAX802 infusions according to the dosing regimen (Table 5)
- Record intraoperative blood loss and transfusion requirements

If the subject has excessive or unexplained bleeding, blood draws for FVIII activity. Treat by whatever means necessary until adequate hemostasis is achieved. If rescue medications become necessary, the subject will subsequently be withdrawn from this BAX802 surgery study.

After the surgical procedure:

- Record the volume of blood loss during surgery and total blood product usage, including salvaged blood, packed red blood cells (pRBCs), platelets, and other blood products
- Assess intraoperative hemostatic efficacy (Part A, Table 2) (at the end of surgery)
- Take sample for FVIII activity within preferably 6 - 8 hours following surgery and within 12 hours at the latest, with dose adjustments as necessary on the day of surgery (see Section 10.5)

If the subject has excessive or unexplained bleeding, blood draws for FVIII activity. Treat by whatever means necessary until adequate hemostasis is achieved. If rescue medications become necessary (see Section 10.5), the subject will subsequently be withdrawn from this BAX802 surgery study.

Table 8: Flow Diagram of Required Procedures for Baxalta Clinical Study 241502

4. Postoperative Procedures (Days 1-13)

- For subjects undergoing major surgery: keep pre-infusion FVIII levels at least at 80% of normal for the first postoperative 72 hours and at least at 50% during postoperative Day 4 to Day 7. From Day 8 until discharge, the FVIII levels should not fall below 30%.
- For subjects undergoing minor surgery: keep pre-infusion FVIII levels at least at 50% of normal for the first postoperative 72 hours. From Day 4 until discharge, the FVIII levels should not fall below 30%.

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

- Record AEs and concomitant medication and non-drug therapy use
- Record blood loss on a daily basis and at drain removal, if applicable
- Record transfusion requirements
- Global Hemostatic Efficacy Assessment (GHEA):
  - Part B (Table 3): assessment of postoperative hemostatic efficacy of BAX802 performed at Day 1 by the operating surgeon/investigator
  - Part C (Table 4): assessment of perioperative hemostatic efficacy of BAX802 at Day 14 performed by the investigator

  If a subject leaves the facility on the day of the surgery/invasive procedure, it is required to have a site visit the next day (Day 1) and at Day 14 to perform the assessments of postoperative (Part B) and perioperative (Part C) hemostatic efficacy, respectively.
- Perform physical examination and vital signs (pulse, respiratory rate, blood pressure and temperature) on Days 1, 2, 3, and 7 post surgery (if a subject remains admitted).
- Blood draws for FVIII activity determination and hematology should be performed coincident with an early morning dose to the greatest extent possible.
- FVIII activity assays at the local and the central laboratories (back-up sample) at least once daily for Days 1 to 13. Additional BAX802 doses will be administered as per Table 5. FVIII activity assays pre infusion (within 30 minutes) and post infusion (15 ±5 minutes) for each IP administration, and at other time points as deemed necessary by the surgeon or investigator throughout the study
  - 1-stage clotting and chromogenic for the central laboratory
  - 1-stage clotting or chromogenic (whichever is available) for local laboratories
- Samples for laboratory testing will be taken daily during Day 1 to 7 post-surgery and then subsequently once weekly:
  - Hematology
  - Clinical chemistry

- If the subject has excessive or unexplained bleeding, blood draws for FVIII activity. Treat by whatever means necessary until adequate hemostasis is achieved. If rescue medications become necessary, the subject will subsequently be withdrawn from this BAX802 surgery study.

Table 8: Flow Diagram of Required Procedures for Baxalta Clinical Study 241502

5. Day 14 ±3 days Visit/Discharge Visit/End of Study [EOS] Visit (Day 42 +7 days)

The Day 14 Visit will be performed 14 days following completion of the surgical procedure, the Discharge Visit will be performed when the subject is discharged, and the EOS Visit will be performed 42 to 49 days following the completion of the surgical procedure. In cases where the Discharge Visit would occur within 3 days of either the Day 14 or the EOS visit, the respective visits will be done as a single visit.

Procedures to be performed for each subject at Day 14 Visit/Discharge Visit/EOS Visit:

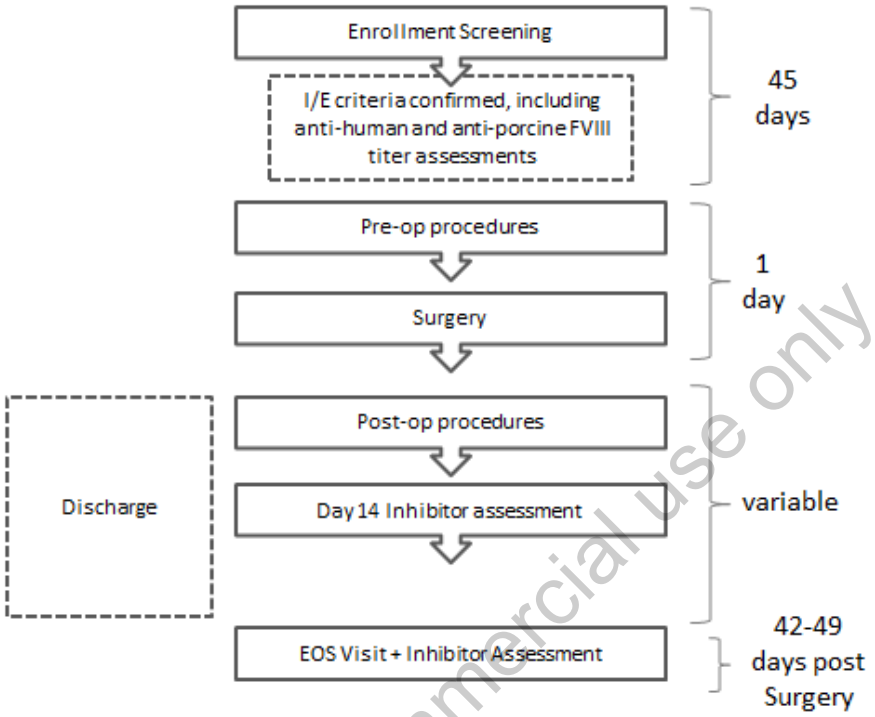
- Perform Postoperative Hemostatic Efficacy Assessment (Part C) on Day 14 by the investigator (hemophilia physician)
- Assessment of blood loss
- Assessment of transfusion requirements
  - Review of concomitant medications/non-drug therapies
  - Complete physical examination
  - AE monitoring
  - Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measure body weight)
- Clinical laboratory assessments (Table 10)
- Immunogenicity assays:
  - Anti-pFVIII and hFVIII binding and inhibitory antibody titers (Note: Before the blood draw for these assessments, at least 72 hours must have elapsed since the previous BAX802 administration).
  - Anti-BHK binding antibody titers

Unrelated Bleeding Episodes During the Postoperative Period:

An intercurrent, unrelated bleeding episode is defined as any bleeding occurring at a different anatomical site than the surgery site during the postoperative period. If these unrelated bleeding episodes occur during the subject's stay in hospital, subjects will be treated with BAX802. If these unrelated bleeding episodes occur after the subject has been discharged, subjects will be treated with BAX802 or with standard of care, as per investigator's discretion. For unrelated bleeding episodes during the postoperative period, assessments will be collected as per Table 11.

20.2 Study Flow Chart

Figure 1: Visit Schedule



20.3 Schedule of Study Procedures and Assessments

Table 9: Schedule of Study Procedures and Assessments

Period	Screening	Preoperative procedures	Intraoperative procedures	Postoperative: Daily procedures; until subject is discharged	Day 14 ±3/ Discharge procedures[a]	End of Study Visit[b]/ Discharge procedures[a]
Procedure/Assessment	Up to 45 days prior to Day 0	Day 0 ~2 hours prior to surgery	Day 0 During surgery	Day 1 to Day 13	Day 14 ±3 Discharge day	Day 42 +7 Discharge day
Eligibility criteria, including medical history[c]	X					
Medications and non-drug therapies	X	X	X	X	X	X
Physical examination	X	X		X[g] (as required)	X	X
Adverse events		X	X	X	X	X
Laboratory assessments[d]	X	X	X	X	X	X
Vital signs[e]	X	X[f]	X[f]	X[f,g]	X	X
Karnofsky Performance Test	X					
Approved FVIII maintenance plan		X				
IP treatment		X (loading dose; Table 5)	X (as required; Table 5)	X (as required; Table 5)	X (as required; Table 5)	
Hemostatic Efficacy Assessments			A as per Table 2	B at 24 hours (Day 1) as per Table 3[h]	C as per Table 4	
Transfusion requirements			X	X	X	X

Continued on Next Page

Continued

[a] In cases where the Discharge Visit would occur within 3 days of either the Day 14 or the End of Study Visit, the respective visits will be done as a single visit.
[b] This visit also applies to subjects who withdraw or discontinue prematurely.
[c] Occurs at enrollment (prior to any study-specific procedures).
[d] For laboratory assessments, see Table 10.
[e] Vital signs will include body temperature, pulse rate, blood pressure, respiratory rate, and weight. Blood pressure will be measured when subjects are in the supine position. Height, measured once at Screening, will also be collected.
[f] Within 30 minutes pre, 15 ±5 minutes post-dose
[g] Perform physical examination and vital signs (pulse, respiratory rate, blood pressure and temperature) on Days 1, 2, 3, and 7 post surgery (if a subject remains admitted).
[h] If the subject is discharged from surgical facility on the day of the procedure, he should attend the site on Day 1 to perform the postoperative hemostatic efficacy assessment. In this case, physical examination, vital signs, laboratory assessments, adverse events, and concomitant medications must also be assessed.

20.4 Clinical Laboratory Assessments

Table 10: Clinical Laboratory Assessments

			Preoperative Period	Postoperative Period			
Period		**Screening**	**Preoperative procedures**	**Intraoperative procedures**	**Postoperative: daily procedures; till subject is discharged**	**Day 14 ±3/ Discharge procedures[a]**	**End of Study Visit[b]/ Discharge procedures[a]**
Assessment	Sample	Up to 45 days prior to Day 0	Day 0 ~2 hours Prior to Surgery	Day 0 During surgery	Day 1 to Day 13	Day 14 ±3 Discharge day	Day 42 +7 Discharge day
FVIII activity (clotting *and* chromogenic assay at central lab; *either* clotting *or* chromogenic assay at local lab)	Citrated plasma	C	L and B within 30 minutes before loading dose, then 15 ±5 minutes after loading dose[c]	Optional sampling, as deemed necessary: L and B Also, if subject has excessive or unexplained bleeding	L and B[d]	L and B	L and B
PT	Citrated plasma	C and L					
Chemistry[e]	Serum	C	L and B	(L)	L Daily Days 1 - 7	C (L)	C (L)
Hematology	Whole blood	C	L	(L)	L Daily Days 1 - 7	C (L)	C (L)
Urinalysis	Urine	C					C
Viral serology[f]	Serum[g]	C					
Anti-pFVIII and hFVIII binding and inhibitory antibody titers	Citrated plasma	C				C (L)[h]	C (L)[h]
Anti-BHK binding Antibody titers	Citrated plasma	C				C (L)	C (L)

Continued on Next Page

Continued

Key: C = central laboratory; L = local laboratory; (L) = local testing optional, to aid in clinical management of patients;
B = back-up sample for central laboratory testing

[a] In cases where the Discharge Visit would occur within 3 days of either the Day 14 or the End of Study visit, the respective visits will be done as a single visit.

[b] This visit also applies to subjects who withdraw or discontinue prematurely.

[c] Surgery may take place only if FVIII is in target range (Table 5).

[d] If underwent major surgery, take sample preferably within 6 to 8 hours following surgery, and within 12 hours at the latest. Sample at least once per day. FVIII activity assays pre infusion (within 30 minutes) and post infusion (15 ±5 minutes) for each IP administration, and at other time points as deemed necessary by the surgeon or investigator throughout the study. Also, if subject has excessive or unexplained bleeding as deemed necessary by the surgeon or investigator.

[e] Sodium, potassium, chloride, bicarbonate, protein, albumin, alanine aminotransferase, bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, and glucose.

[f] HIV-1 and HIV-2 antibody, HBsAb, HBsAg, HBcAb, and HCV Ab, CD4 for HIV positive patients and HCV-RNA or HIV-RNA for confirmatory testing of HIV or HCV positive results, respectively.

[g] Citrated plasma for HCV-RNA or HIV-RNA confirmatory testing.

[h] Before the blood draw for these assessments, at least 72 hours must have elapsed since the previous BAX802 administration.

20.5 Schedule of Study Procedures and Clinical Laboratory Assessments for Unrelated Bleeding Episodes in the Postoperative Period

Table 11: Schedule of Study Procedures and Assessments for Unrelated Bleeding Episodes

Period	Sample (for lab assessments)	In-hospital or Unscheduled Visit[a]	Follow-up Visits At 24 ±2 hours after the initiation of treatment and At the resolution of bleed (if not resolved within 24 hours)
Procedure/Assessment		Day 1 to End of Study Visit	As required
Medications and non-drug therapies		X	X
Physical examination		X	X
FVIII activity (clotting *and* chromogenic assay at central lab; *either* clotting *or* chromogenic assay at local lab)	Citrated plasma	L and B within 30 minutes before BAX802 dose, then 15 ± 5 min after dose[b]	L and B[b]
Anti-pFVIII binding and inhibitory antibody titers	Citrated plasma	C (L)	
Vital signs		X[c]	X[c]
IP treatment[d]		X (as required; Table 6)	X (as required; Table 6)
Hemostatic Efficacy Assessments		X as per Table 7	X as per Table 7
Adverse events		X	X
Transfusion requirements		X	X

Key : C = central laboratory; L = local laboratory; (L) = local testing optional, to aid in clinical management of patients;
B = back-up sample for central laboratory testing

[a] If the unrelated bleeding episode occurs after subject's discharge, subject will visit the investigator and will be treated with BAX802 or with Standard of Care, as per investigator's discretion. If these unrelated bleeding episodes occur during the subject's stay in hospital, subjects will be treated with BAX802 (Note: BAX802 will not be used to treat these bleeding episodes if the Day 14 anti-pFVIII titer [if available] is > 10 BU).

[b] If another dose of BAX802 is necessary, an additional post-infusion FVIII activity determination must be performed 15 ±5 minutes following the infusion.

[c] Within 30 minutes pre-dose, 15 ±5 minutes post-dose.

[d] If Day 14 anti-pFVIII titers and hematocrit are not available, the Screening lab results shall be used to make dosing calculations rather than waiting for Day 14 results..

20.6 Global Efficacy Assessments Scores

Table 12: Combinations of Individual Efficacy Assessments (A, B, C) and GHEA Score

Individual Assessment Scores (A,B,C)	GHEA
3 3 3	Excellent
3 3 2	Excellent
3 2 2	Excellent
3 3 1	Good
3 2 1	Good
3 1 1	Good
2 2 2	Good
2 2 1	Good
2 1 1	Fair
1 1 1	Fair
3 3 0	None
3 2 0	None
3 1 0	None
3 0 0	None
2 2 0	None
2 1 0	None
2 0 0	None
1 1 0	None
1 0 0	None
0 0 0	None

20.7 Definitions

20.7.1 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.

20.7.2 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.[5,21]

21. REFERENCES

1. Coppola A, Di Capua M, Di Minno MND et al. Treatment of hemophilia: A review of current advances and ongoing issues. J.Blood Med. 2010;1:183-195.
   Link to Publisher´s Site:
   http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3262316/pdf/jbm-1-183.pdf

2. Janbain M, Leissinger CA, Kruse-Jarres R. Acquired hemophilia A: emerging treatment options. J.Blood Med. 2015;6:143-150.
   Link to Publisher´s Site:
   http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4431493/pdf/jbm-6-143.pdf

3. Mansouritorghabeh H. Clinical and laboratory approaches to hemophilia A. Iran.J.Med.Sci. 2015;40:194-205.
   Link to Publisher´s Site:
   http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4430880/pdf/ijms-40-194.pdf

4. Berntorp E, Shapiro A, Astermark J et al. Inhibitor treatment in haemophilias A and B: summary statement for the 2006 international consensus conference. Haemophilia. 2006;12 Suppl 6:1-7.

5. World Federation of Hemophilia Treatment Guidelines Working Group. Guidelines for the management of hemophilia 2nd Edtion. 76. 2005. World Federation of Hemophilia (WFH).
   Link to Publisher´s Site: http://www1.wfh.org/publication/files/pdf-1472.pdf

6. Santagostino E, Escobar M, Ozelo M et al. Recombinant activated factor VII in the treatment of bleeds and for the prevention of surgery-related bleeding in congenital haemophilia with inhibitors. Blood Rev. 2015;29 Suppl 1:S9-S18.

7. Valentino LA, Cooper DL, Goldstein B. Surgical experience with rFVIIa (NovoSeven) in congenital haemophilia A and B patients with inhibitors to factors VIII or IX. Haemophilia. 2011;17:11-579.

8. Kempton CL, White GC, II. How we treat a hemophilia A patient with a factor VIII inhibitor. Blood. 2009;113:11-17.

9. Kasper CK. Effect of prothrombin complex concentrates on factor VIII inhibitor levels. Blood. 1979;54:1358-1368.

10. Young G, Sørensen B, Dargaud Y et al. Thrombin generation and whole blood viscoelastic assays in the management of hemophilia: current state-of-art and future perspectives. Blood. 2013;121:1944-1950.

11. Kempton CL, Abshire TC, Deveras RA et al. Pharmacokinetics and safety of OBI-1, a recombinant B domain-deleted porcine factor VIII, in subjects with haemophilia A. Haemophilia. 2012;18:798-804.

12. Mahlangu J, Andreeva T, Macfarlane D et al. A phase II open-label study evaluating the hemostatic activity, pharmacokinetics and safety of recombinant porcine factor VIII (OBI-1) in hemophlia A patients with inhbitors directed against human FVIII [abstract]. Haemophilia. 2008;14 Suppl 2:15-16.

13. Kruse-Jarres R, St Louis J, Greist A et al. Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A. Haemophilia. 2015;21:162-170.

14. Baxter Healthcare Corporation. Obizur core data sheet. 7-22-2015.

15. Brettler DB, Forsberg AD, Levine PH et al. The use of porcine factor VIII concentrate (Hyate:C) in the treatment of patients with inhibitor antibodies to factor VIII. A multicenter US experience. Arch.Intern.Med. 1989;149:1381-1385.

16. Hay CRM, Lozier JN, Lee CA et al. Safety profile of porcine factor VIII and its use as hospital and home-therapy for patients with haemophilia-A and inhibitors: the results of an international survey. Thromb.Haemost. 1996;75:25-29.

17. Baxter Healthcare Corporation. Package Insert: OBIZUR [antihemophilic factor (recombinant), porcine sequence] lyophilized powder for solution for intravenous injection. 10. 2014. OBIZUR.

18. Lee CA. The evidence behind inhibitor treatment with porcine factor VIII. Pathophysiol.Haemost.Thromb. 2002;32 Suppl 1:5-8.

19. Kasper, C. Diagnosis and Management of Inhibitors to Factors VIII and IX - An Introductory Discussion for Physicians. Treatment of Hemophilia(34), 22. 2004. World Federation of Hemophilia (WFH).
Link to Publisher´s Site: http://www1.wfh.org/publications/files/pdf-1178.pdf

20. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, ed. Evaluation of Chemotherapeutic Agents. New York: Columbia University Press; 1949:191-205.

21. Blanchette VS, Key NS, Ljung LR et al. Definitions in hemophilia: Communication from the SSC of the ISTH. J.Thromb.Haemost. 2014;12:1935-1939.

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: BAX802

STUDY TITLE: A Phase 3, Multicenter, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX802) in the Treatment of Patients with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures

PROTOCOL IDENTIFIER: 241502

CLINICAL TRIAL PHASE 3

ORIGINAL: 2015 SEP 30

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: to be determined
IND NUMBER: to be determined

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: BAX802

STUDY TITLE: A Phase 3, Multicenter, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX802) in the Treatment of Patients with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures

PROTOCOL IDENTIFIER: 241502

CLINICAL TRIAL PHASE 3

ORIGINAL: 2015 SEP 30

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: to be determined
IND NUMBER: to be determined

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

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD
[redacted], Clinical Development

CLINICAL STUDY PROTOCOL

PRODUCT: BAX 802

STUDY TITLE:
A Phase 3, Multicenter, Single-arm, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX 802) in Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures

STUDY SHORT TITLE: BAX 802 in Congenital Hemophilia A with Inhibitors

PROTOCOL IDENTIFIER: 241502

CLINICAL TRIAL PHASE 3

AMENDMENT 1: 2016 FEB 03

Replaces: ORIGINAL: 2015 SEP 30

ALL VERSIONS:
Amendment 1: 2016 FEB 03
Original: 2015 SEP 30

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: to be determined
IND NUMBER: to be determined

Study Sponsor(s):

Baxalta US Inc.
One Baxter Way
Westlake Village, CA 91362,
UNITED STATES

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna,
AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted], Clinical Development
Baxalta US Inc.

1.2 Study Organization

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

2. SERIOUS ADVERSE EVENT REPORTING

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

ALL SAEs ARE TO BE REPORTED ON THE 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 REQIREMENT.

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:

1. AE, Section 12.1
2. SAE, Section 12.1.1.1
3. Assessment of AEs, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	BAX 802
Name(s) of Active Ingredient(s)	Recombinant Porcine Factor VIII
CLINICAL CONDITION(S)/INDICATION(S) Congenital hemophilia A (CHA) patients with inhibitors to FVIII undergoing surgical and other invasive procedures	
PROTOCOL ID	241502
PROTOCOL TITLE	A Phase 3, Multicenter, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX 802) in Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures
Short Title	BAX 802 in CHA with Inhibitors
STUDY PHASE	Phase 3
PLANNED STUDY PERIOD	
Initiation	2016, FEB
Primary Completion	2017, DEC
Study Completion	2017, DEC
Duration	20 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose To evaluate the efficacy and safety of BAX 802 in males with CHA with inhibitors who are undergoing major or minor elective surgical, dental, or other invasive procedures.	
Primary Objective To evaluate the perioperative hemostatic efficacy of BAX 802 in male subjects with CHA with inhibitors to human factor VIII (hFVIII) undergoing major or minor elective surgical, dental, or other invasive procedures as determined by the Global Hemostatic Efficacy Assessment (GHEA) score.	
Secondary Objectives 1. To determine the safety of BAX 802 used in the perioperative setting by assessing: • The development of and change in titer of anti-pFVIII and anti-hFVIII inhibitory antibodies (binding and neutralizing), and development of binding antibodies to baby hamster kidney (BHK) proteins • The occurrence of thrombotic events and/or allergic reactions to BAX 802 • The occurrence of adverse events (AEs) related to BAX 802 • The occurrence of clinically significant changes in vital signs and routine laboratory parameters related to BAX 802	

2. To determine the intra- and postoperative and overall perioperative blood loss at the end of surgery, compared to the estimated volume of expected average and maximum blood loss in a comparable healthy individual as predicted preoperatively by the investigator/surgeon
3. To determine the daily and total weight-adjusted administration of BAX 802 per subject
4. To determine the blood product utilization
5. To determine the occurrence of bleeding episodes during the intra- and postoperative periods and additional need for surgical intervention
6. To evaluate any unrelated bleeding episodes in the postoperative period.

STUDY DESIGN

Study Type/ Classification/ Discipline	Efficacy and Safety
Control Type	No control
Study Indication Type	Treatment
Intervention model	single-group
Blinding/Masking	Open-label
Study Design	This study is a Phase 3, prospective, open-label, uncontrolled, multicenter study to evaluate the efficacy and safety of BAX 802 in at least 10 surgeries in 10 evaluable male subjects with CHA with inhibitors to hFVIII who are undergoing major and minor surgical, dental or other invasive procedures. At least 5 of the procedures must be major surgeries in 5 evaluable subjects.
Planned Duration of Subject Participation	The duration of subject participation depends on the nature of the invasive procedure: it will run from the signing of the informed consent until completion of the End of Study Visit (at least 6 weeks post-surgery [Day 0]).

Primary Outcome Measure

The primary outcome measure is the GHEA score, which is composed of 3 individual ratings:

- Assessment of intraoperative hemostatic efficacy of BAX 802 performed by the operating surgeon
- Assessment of postoperative hemostatic efficacy of BAX 802 at postoperative Day 1 (approximately 24 hours after surgery) performed by the operating surgeon
- Assessment of overall perioperative hemostatic efficacy of BAX 802 at Day 14 or discharge (whichever is earlier), performed by the investigator.

The scores of each of the 3 individual ratings described above, will be added together to form a GHEA score.

Secondary Outcome Measures

Efficacy

1. Blood loss compared to the estimated volume of expected average blood loss and expected maximum blood loss in a comparable healthy individual as predicted preoperatively by the investigator/surgeon at the following time points:
   - Intraoperative, at the end of surgery
   - Postoperative Day 1, approximately 24 hours after surgery
   - Overall perioperative Day 14 or discharge (whichever is earlier)
2. Daily and total weight-adjusted administration of BAX 802 per subject
3. Volume of blood, red blood cells, platelets, and other blood products transfused
4. Occurrence of bleeding episodes during the intra- and postoperative periods and additional need for surgical intervention
5. Efficacy of the treatment of unrelated bleeding episodes in the postoperative period.

Safety

1. Development of, and changes to, the titer of inhibitory and binding antibodies to recombinant porcine factor VIII (rpFVIII)
2. Development of, and changes to, the titer of inhibitory and binding antibodies to hFVIII
3. Development of binding antibodies to BHK proteins
4. Occurrence of thrombotic events
5. Incidence of severe allergic reactions (eg, anaphylaxis)
6. Incidence of other IP-related AEs
7. Incidence of clinically significant changes in vital signs and routine laboratory parameters (hematology, clinical chemistry)

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form:** Injectable Reconstituted Solution **Dosage frequency:** PRN = as needed **Mode of Administration:** intravenous infusion
SUBJECT SELECTION	
Targeted Accrual	Enroll 10 evaluable subjects
Number of Groups/Arms/Cohorts	1 arm

Inclusion Criteria

1. Subject is ≥ 18 to ≤ 65 years old at the time of screening
2. Subject has provided signed informed consent
3. Subject has severe (FVIII level < 1%) or moderately severe (FVIII level ≤ 2%) CHA with inhibitors to human FVIII, as tested at screening at the central laboratory
4. Subject requires elective surgery or other invasive procedures
5. Subject is not currently receiving or has recently received (< 30 days) ITI therapy
6. Subject has a Karnofsky performance score of ≥ 60
7. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm3 at screening
8. Subject is hepatitis C virus negative (HCV-) by antibody or polymerase chain reaction (PCR) testing; or HCV+ with chronic stable hepatitis disease
9. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

1. The subject requires emergency surgery
2. The subject's weight is < 35 kg or > 120 kg
3. Clinically symptomatic liver disease (eg, ≥ 5 X upper limit of normal alanine aminotransferase [ALT], as confirmed by central laboratory at screening, clinical evidence of portal hypertension, severe hypoalbuminemia or a documented prothrombin time/international normalized ratio [PT/INR] > 1.5)
4. Clinically symptomatic renal disease (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening
5. Anti-porcine inhibitor > 10 Bethesda units (BU) prior to surgery
6. Platelet count < 100,000/µL
7. Subject has another active coagulation disorder, other than hemophilia A, as per the medical history
8. Planned use of α-interferon with or without ribavarin for HCV infected patients or planned use of a protease inhibitor for HIV-infected patients. Patients currently taking any of these medications for ≥ 30 days are eligible
9. Known hypersensitivity to rpFVIII, or hamster or murine proteins
10. Subject has been exposed to an IP 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
11. Unable to tolerate quantity of blood to be drawn for protocol procedures
12. Subject is a family member or employee of the investigator

STATISTICAL ANALYSIS

Sample Size Calculation

The sample size of at least 10 surgeries in 10 evaluable male subjects (at least 5 major surgeries in 5 evaluable subjects), as defined in the protocol, was chosen to provide sufficient evidence of safety and effectiveness for this indication and is not based on statistical considerations.

Planned Statistical Analysis

Analysis Sets

The safety analysis set (SAS) will be comprised of all subjects who received any amount of BAX 802. The full analysis set (FAS) will be comprised of all surgeries with at least 1 available hemostatic assessment. The per-protocol analysis set (PP) will be comprised of all surgeries with evaluable ratings for all 3 perioperative hemostatic efficacy assessments, whom subjects met all study entry criteria and had no major protocol violations that might impact hemostatic efficacy assessments.

Primary Outcome Measure

The primary efficacy measure will be the overall assessment of hemostatic efficacy assessed intraoperatively by the surgeon and postoperatively by the investigator (hemophilia physician) at postoperative Day 1 (ie, the day following the day of surgery) and perioperatively at postoperative Day 14 visit or discharge (whichever is earlier), and will be summarized by the GHEA score and rated "excellent", "good", "fair" and "none".

A treatment success will be defined as a rating of excellent and/or good.

Owing the possibility of multiple surgeries per subject, the statistical entity on which the primary outcome measure will be reported is the surgery.

Point estimates and corresponding 2-sided exact confidence intervals (CIs) at the 90% confidence level will be calculated for the rate of hemostatic efficacy assessments with excellent/good outcome.

The primary efficacy analysis will be based on the FAS population. As a supportive analysis, the same calculations will also be carried out on the PP population.

Any blood loss which is considered as unrelated bleeding (defined as any bleeding occurring at a different anatomical site other than the surgery site during the postoperative period) will not be taken into account for while making assessment of hemostatic efficacy for the primary efficacy measure.

Secondary Outcome Measures

Secondary hemostatic efficacy analysis:

Where possible, secondary outcome measures will be reported at the surgery level rather than the subject level. Descriptive statistics will be used to summarize the actual blood loss and transfusion requirements.

The summary of average daily and total weight-adjusted doses (average through postoperative Day 14 or discharge [whichever is earlier]) of BAX 802 per subject as well as the occurrence of bleeding episodes will be provided using descriptive statistics.

For unrelated bleeding episodes in the postoperative period, descriptive statistics will be used to summarize the overall hemostatic efficacy rating at 24 ±2 hours after initiation of treatment and at resolution of bleed. The secondary efficacy analysis will be performed on the FAS only. Separate descriptive summaries of average daily and total weight-adjusted doses required to treat unrelated bleeding episodes and will be provided.

Safety Analysis

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by presenting the number and percentage of subjects having any AE, having an AE in each system organ class, and having each individual AE as reported by preferred term. In the summaries, AEs will be counted only once per patient. If a patient reports the same AE more than once, it will be counted with its worst severity and closest relationship to the study product.

The number of subjects who experienced serious adverse events (SAEs) and the number of SAEs will be tabulated. In addition, the number of subjects who experienced AEs related to IP and the number of IP related AEs will be tabulated and subcategorized for thrombotic events, inhibitory and total binding antibodies to rpFVIII and hFVIII, and binding antibodies to BHK proteins.

An overview table for AEs will be provided, presenting the number of AEs, the number of subjects with AEs and the corresponding percent of subjects in total, and by seriousness and relationship to study treatment. An additional summary table will present the total number of (mild, moderate, severe) AEs by system organ class and preferred term with relationship to IP.

Summary statistics over time will be presented for the continuous laboratory parameters. Descriptive statistics of changes from baseline (Day 0 - prior to surgery) by study visits will also be presented.

A frequency table of results of categorical laboratory parameters will be produced. Furthermore, laboratory abnormalities will be analyzed by shift tables where each subject will be counted only once with the worst grade in the summary tables.

Vital signs assessments as well as the corresponding changes from baseline will be summarized descriptively at each scheduled assessment.

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AICC	anti-inhibitor coagulant complex
ALT	alanine aminotransferase
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
B19V	parvovirus B19
BHK	baby hamster kidney
BU	Bethesda units
CI	confidence interval
CHA	Congenital Hemophilia A
CRF	case report form
CRO	Contract Research Organization
EC	ethics committee
EBL	estimated blood loss
eCRF	electronic case report form
EDC	electronic data capture
FAS	full analysis Set
GCP	Good Clinical Practice
GHEA	Global Hemostatic Efficacy Assessment
HAV	hepatitis A virus
HBV	hepatitis B virus
Hct	hematocrit
HCV	hepatitis C virus
HEV	hepatitis E virus
hFVIII	human factor VIII
HIV	human immunodeficiency virus
IB	Investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IP	investigational product
IPC	intermittent pneumatic compression

Abbreviation	Definition
ISMC	internal safety monitoring committee
ITI	immune tolerance induction
LMWH	low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
NMC	Non-medical complaint
OR	operating room
PCR	polymerase chain reaction
pFVIII	porcine factor VIII
PP	Per Protocol (analysis set)
PRN	"pro re nata" (as needed)
PT/INR	prothrombin time/international normalized ratio
PV	plasma volume
rhFVIII	recombinant human factor VIII
rpFVIII	recombinant porcine factor VIII
RSI	Reference Safety Information
SAE	serious adverse event
SAER	serious adverse event report
SAP	statistical analysis plan
SAS	safety analysis set
SIC	subject identification code
TGA	thrombin generation assays
VIIa	activated factor VII
WFH	World Federation of Hemophilia

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

The investigational product (IP), BAX 802, is a recombinant form of porcine factor VIII (rpFVIII) from which the B domain has been deleted. Deletion of the B domain does not affect the safety or efficacy of this recombinant form of human factor VIII (rhFVIII) in the treatment of hemophilia A. BAX 802 (rpFVIII) is being developed for the perioperative management of hemostasis in subjects with congenital hemophilia A (CHA) with inhibitors to human factor VIII (hFVIII) undergoing surgical or other invasive procedures. This rpFVIII was approved by the United States Food and Drug Administration (FDA) in 2014 for the treatment of bleeding episodes in adults with acquired hemophilia A (AHA; non hemophilia subjects developing spontaneous autoantibody inhibitors to hFVIII) under the trade name OBIZUR®.

6.2 Clinical Condition/Indication

Congenital hemophilia A is a congenital bleeding disorder caused by a deficiency or complete absence of coagulation factor VIII (FVIII)[1] and is referred to as CHA in order to differentiate it from AHA, which is a rare autoimmune disease with different bleeding patterns caused by immunoglobulin G antibodies that bind to specific domains on the FVIII molecule, in a person with a negative personal or family history of a coagulopathy.[2]

Overall, CHA accounts for about 80% of hemophiliacs. It affects all ethnic populations and its prevalence varies among different countries, but is estimated at a rate of 3 to 20 cases per 100,000 population. The World Federation of Hemophilia (WFH) has estimated the total number of hemophilia cases at about 500,000 universally, of which one-third are diagnosed. The tendency to bleed in these subjects correlates with the plasma level of FVIII. This lifelong disorder has 3 clinical phenotypes (severe, moderate, and mild) that correlate with FVIII levels in plasma (< 1%, 1 to 5%, and 5 to 30%, respectively).[3]

Subjects with hemophilia A typically develop recurrent bleeding episodes. The most effective approach for treatment of acute bleeding episodes in subjects with hemophilia A is hFVIII replacement therapy.[4, 5] However, a major complication in the treatment of subjects with hemophilia A is the development of neutralizing antibodies (inhibitors) to hFVIII, which impair the efficacy of replacement therapy with hFVIII concentrates. Inhibitor development occurs more frequently among patients with severe or moderately severe hemophilia, and approximately 30% of patients with severe CHA develop

inhibitors. In CHA patients with high-responding inhibitors, standard replacement therapy with FVIII concentrates is usually ineffective, resulting in poor control of hemorrhagic episodes. This in turn increases the risk of morbidity, mortality, orthopedic complications and disability, as well as reduced quality of life, compared with patients without inhibitors.[6] Patients with CHA with inhibitors are also at risk of perioperative bleeding complications, since replacement of the missing coagulation factor is ineffective, presenting a therapeutic challenge in elective or emergency surgery.[7]

Currently Available Treatments and Unmet Medical Need

In CHA patients with transient, low-responding and/or low-titers (< 5 Bethesda units [BU]/mL) inhibitors, increased doses of FVIII may be sufficient to overcome the inhibitor and provide hemostasis. In CHA patients with high-responding inhibitors (> 5 BU/mL), standard replacement therapy with FVIII concentrates is usually ineffective, resulting in poor control of hemorrhagic episodes.

Alternative therapies are required for subjects with inhibitors who no longer respond to hFVIII replacement therapy. Recombinant activated factor VII (rFVIIa, NovoSeven®) and FEIBA (FVIII inhibitor bypassing activity; anti-inhibitor coagulant complex [AICC]) bypass the normal coagulation cascade and hence the FVIII inhibitors, and are therefore referred to as bypassing agents. Although these agents are able to manage bleeding in the presence of inhibitors, they do not attempt to restore the normal pathways of hemostasis, but instead boost thrombin generation despite a lack of platelet-surface FVIIIa–FIXa ('tenase') activity.[6] The measurement of levels of factor VIIa in the subject's plasma cannot be used as a clinically relevant surrogate marker and does not correlate with clinical outcome. Without an adequate biomarker, the dosage and treatment schedule cannot be clearly defined.[8] In addition, the response to rFVIIa treatment may be inconsistent both from subject to subject and between different bleeds in the same subject. Because FEIBA is a human plasma fraction containing several coagulation factors, it has the potential to transmit human pathogens and may also cause thromboembolic events. Since the plasma fraction also contains hFVIII, it has been associated with a rise in hFVIII antibodies in approximately 20% of subjects.[9] Moreover, as with rFVIIa, there is no validated biomarker that correlates with the clinical outcome with FEIBA treatment, although both thrombin generation assays (TGA) and whole blood viscoelastic assays have been evaluated for this purpose with some success.[10]

The ultimate goal of treatment for these patients is eradication of the inhibitor through immune tolerance induction (ITI), which involves frequent and long-term administration of factor concentrates in an attempt to build tolerance in the immune system to FVIII or factor IX, and thus restore responsiveness to factor replacement therapy. However, ITI fails in approximately 30% of inhibitor patients with CHA.[6]

There is therefore a clinical need for an effective hemostatic agent for use in subjects with CHA who have inhibitors to hFVIII, and which allows monitoring of hemostatic efficacy based upon measurement of plasma FVIII activity levels, thus facilitating early determination of clinical benefit and the patient's clinical status.

6.3 Population to be Studied

The study population will comprise of at least 10 surgeries in 10 evaluable male subjects with CHA with inhibitors to hFVIII undergoing major or minor elective surgical, dental, or other invasive procedures (at least 5 major surgeries in 5 evaluable subjects). Adult (≥ 18 and ≤ 65 years) male subjects will be considered to be eligible provided that they satisfy all of the inclusion criteria listed in Section 9.1 and none of the exclusion criteria listed in Section 9.2.

6.4 Findings from Nonclinical and Clinical Studies

6.4.1 Finding from Nonclinical Studies

Nonclinical studies were performed with rpFVIII to demonstrate hemostatic activity in 2 animal models of hemophilia A (mice and dogs), local and systemic tolerance in a range of doses in single or repeat dose toxicology studies in monkeys, pharmacokinetics (PK) in dogs and monkeys, and immunogenicity in mice and monkeys.

Compatibility with the usual injection materials (needles, plastic syringes, and butterfly infusion needles with tubing) has been demonstrated. Studies in monkeys demonstrated the tolerability of repeated single daily injections of rpFVIII at doses up to 1000 U/kg, with injections at each dose level given once daily for 7 days. In 2 animal models of hemophilia A (mice and dogs), the hemostatic activity of rpFVIII was studied in comparison with Hyate:C. The rpFVIII was found to be efficacious in a dose-related fashion in controlling the bleeding associated with a standardized hemorrhagic insult. No animal studied was observed to have had an acute reaction to the injection of rpFVIII.

6.4.2 Findings from Clinical Studies

The safety and efficacy of rpFVIII was explored in 4 clinical trials prior to marketing approval:

- OBI-1-101: a Phase I, multicenter, randomized, double-blinded, double-dummy, parallel-group, comparison of the safety, tolerance, and PK study of rpFVIII versus Hyate:C was conducted.[11]
- OBI-1-201: a Phase II, prospective, open-label, non-comparative study was conducted to assess the hemostatic activity of rpFVIII. Eligible subjects had a clinical diagnosis of hemophilia A with inhibitors to hFVIII, an anti-pFVIII inhibitor antibody titer < 20 BU at screening, and an uncomplicated joint or soft tissue bleed, or other non-life threatening and non-limb threatening bleeding episode.[12]
- OBI-1-301: a multicenter, open-label, single-cohort, prospective, Phase II/III study of rpFVIII in subjects with acquired hemophilia to determine the hemostatic efficacy and safety of rpFVIII in the control of serious bleeding episodes.[13]
- OBI-1-302: a prospective, non-randomized, open-label study designed to assess treatment of serious bleeding episodes with rpFVIII in subjects with CHA who had developed anti-hFVIII inhibitors; this study was terminated by the sponsor after 1 subject was treated for administrative reasons, not due to safety or lack of efficacy concerns.

In all clinical studies, rpFVIII was generally well tolerated. There were no drug-related AEs reported in subjects who received rpFVIII in the Phase I study. One subject in the Phase II study (OBI-1-201) experienced pruritus (that resolved with diphenhydramine) that was possibly related to study drug. This AE occurred during the first bleeding episode, but the subject did not have a reaction during a second rpFVIII treated bleeding episode. In the Phase I and Phase II studies, no AEs led to treatment interruption, discontinuation from the study, or death. Vital signs, laboratory values, medical history and physical examination findings were within normal parameters for both studies and raised no safety concerns.

In the Phase II study (OBI-1-201), the ITT Population consisted of 9 male subjects with CHA and with an inhibitor antibody to hFVIII. Six of the subjects (67%) were black and 3 subjects (33%) were Caucasian. The mean age of the subject population was 23.7 years (Range: 14 to 34). The primary efficacy objective of the study was to evaluate the hemostatic efficacy of rpFVIII in the treatment of non-life/non-limb threatening bleeds in subjects with CHA and inhibitors.

A total of 25 bleeds in 9 subjects were treated with rpFVIII and all bleeds were successfully controlled with 8 or less injections of rpFVIII. The median number of rpFVIII injections administered per bleeding episode was 1.0 (Range: 1 to 8) and the median time from bleeding onset to treatment was 5.67 hours (range: 1.5 to 20.0 hours). Across all bleeding episodes the median total dose of rpFVIII per bleeding episode was 224.1 U/kg (range: 50.0 to 1066.4 U/kg). The median initial Treatment Dose (including the Loading Dose if applicable), was 159 U/kg (Range: 50 to 576 U/kg) and resulted in a median increase of FVIII plasma level of 16 % with the 1-stage clotting assay (Range: 0.5 to 427 %) and a median increase of 17% with the chromogenic assay (Range: 0 to 248 %). Twenty of the 25 (80%) bleeds were controlled within 6 hours having been administered 1 Treatment Dose of rpFVIII. For those 20 bleeds controlled with 1 Treatment Dose (including the Loading Dose if applicable), the median dose was 200.8 U/kg. rpFVIII was well tolerated and of the reported AEs (n=61) only 18 were considered treatment emergent. Two subjects reported an AE that was possibly related to study drug. One AE of itching/pruritus during the first bleeding episode but without reaction during a second rpFVIII treated bleeding episode. The second AE was a report of increased ALT and AST, possibly associated with a confirmed Hepatitis C infection, while it was uncertain whether the corresponding blood sample was taken before or after rpFVIII administration. Three subjects suffered treatment emergent SAEs but none were considered related to study drug. No reported AE led to treatment interruption, discontinuation from the study or death. Eight out of 9 (8/9, 89%) subjects developed anti-pFVIII antibodies following exposure to rpFVIII. In subjects that received repeated rpFVIII treatment, higher anti-pFVIII titers did not affect efficacy or safety and no increase in AEs or bleeding episodes were reported in the subjects with the highest titers. Regardless of the observed anti-pFVIII titers at pre-treatment or the obtained FVIII recovery values after treatment initiation, all bleeding episodes were successfully controlled. Analyses of baby hamster kidney (BHK; host cell line) antibody levels indicated that no subjects produced detectable levels of antibodies against BHK.

In the prospective, open-label trial (OBI-1-301), the efficacy of rpFVIII for the treatment of serious bleeding episodes in subjects with AHA was investigated. The trial was conducted in 18 Caucasian, 6 African-American, and 5 Asian subjects diagnosed with AHA, having auto-immune inhibitory antibodies to hFVIII, and experiencing serious bleeding episodes that required hospitalization. Subjects with a prior history of bleeding disorders other than AHA, anti-pFVIII antibody titer > 20 BU, or in whom the bleeding episode was judged likely to resolve on its own, were excluded. One subject was considered evaluable at study entry; however, it was later determined that this subject did not have AHA, leaving 28 subjects evaluable for efficacy.

Of the 28 subjects evaluable for efficacy, all subjects had a positive response to treatment for the initial bleeding episodes at 24 hours after dosing. A positive response was observed in 95% (19/20) of subjects evaluated at 8 hours and 100% (18/18) at 16 hours. In addition to response to treatment, the overall treatment success was determined by the investigator based on his/her ability to discontinue or reduce the dose and/or dosing frequency of rpFVIII. A total of 24/28 subjects (86%) had successful treatment of the initial bleeding episode. Of those subjects treated with rpFVIII as first-line therapy, defined as no immediate previous use of anti-hemorrhagic agents prior to the first rpFVIII treatment, 16/17 subjects (94%) had eventual treatment success reported. Eleven subjects were reported to have received anti-hemorrhagics (eg. rFVIIa, activated prothrombin-complex concentrate, tranexamic acid) prior to first treatment with rpFVIII. Of these 11 subjects, 8 had eventual successful treatment (73%). No related serious adverse reactions occurred. Non-serious adverse events related to treatment were noted and assessed by the investigator in 6/29 subjects (20.7%). One subject had mild tachycardia, hypotension and constipation. One subject had 2 instances of mild PICC line occlusion. One subject had a mild hypofibrogenemia and 1 subject had moderate mental status changes. All of these adverse effects completely resolved. Two subjects developed anti-porcine FVIII (pFVIII) inhibitors after infusion of study drug (range 8 to 51 BU) and were discontinued from treatment; however both subjects had a positive response to treatment at the 24 hour primary endpoint assessment. An investigation was conducted by the sponsor and, in summary, the 2 incidences of anti-pFVIII inhibitors were considered related to rpFVIII treatment, while the other non-serious treatment-related adverse events were considered as unlikely to be related to rpFVIII. Anti-pFVIII inhibitors were detected prior to infusion in 10/29 patients (range 0.8 to 29 BU). All of these subjects had a positive response at 24 hours post-rpFVIII first infusion. No anti-BHK antibodies were observed in any of the 29 treated subjects.

At the time of OBIZUR® marketing approval, the clinical trial data indicated that rpFVIII was well tolerated and had demonstrated effectiveness in the control of bleeding in study subjects. As of 2015 December 31, there have been 4 post-marketing spontaneous serious adverse event reports. The reports were considered possibly associated and consistent with the known safety profile of OBIZUR®.[14]

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

Porcine FVIII (Hyate:C), derived from porcine plasma, had been used successfully starting in the 1980s to achieve hemostasis in the presence of anti-hFVIII inhibitors, as the antibodies generally have low immunological cross-reactivity with pFVIII.[15] However, the number of hemophilia A subjects who were appropriate candidates to receive Hyate:C was limited by the degree to which their anti-hFVIII antibodies cross-reacted with pFVIII and the presence of any anti-pFVIII inhibitors. While a median inhibitor cross-reactivity observed to porcine VIIIC was only 15%, an absent, intermediate, or brisk specific anti-porcine anamnestic response was observed in 29%, 40%, and 31% of patients, respectively.[16] The commercial production of Hyate:C was discontinued in 2005 due to problems with sourcing suitable porcine plasma, but not due to any safety or efficacy concerns.

BAX 802 is a B-domain deleted rpFVIII glycoprotein which is being developed for the perioperative management of hemostasis in subjects with CHA with FVIII inhibitors undergoing surgical or other invasive procedures. B-domain deleted rpFVIII glycoprotein has been extensively studied. BAX 802 (as marketed OBIZUR®) is not currently indicated for the treatment of CHA.[17]

OBIZUR® was approved based on the safety and efficacy data from 28 subjects with AHA treated with B-domain deleted rpFVIII glycoprotein in the Phase 2/3 open-label clinical study OBI-1-301. The safety, hemostatic activity, and PK profile of B-domain deleted rpFVIII glycoprotein was also supported by results of an open-label Phase 2 study in patients with CHA with inhibitors (CSR OBI-1-201), and a randomized Phase 1 study comparing B-domain deleted rpFVIII glycoprotein with a plasma-derived pFVIII (CSR OBI-1-101).

The data supported the use of B-domain deleted rpFVIII glycoprotein to treat serious bleeding episodes in AHA patients (Section 6.4.2). It was demonstrated that B-domain deleted rpFVIII glycoprotein provides benefit to AHA patients who are unresponsive to alternative agents with an improved dosing algorithm. It was possible to monitor hemostatic efficacy based upon measurement of plasma FVIII activity levels, thus facilitating early determination of clinical benefit and the patient's clinical status. An additional benefit to the patient was that it was possible to adjust the dose based on the FVIII levels rather than follow fixed dosing, ensuring that adequate doses were administered to achieve hemostasis.

The most frequently reported adverse reaction in patients with AHA was the development of inhibitors to pFVIII.[17]

Overall, efficacy and safety clinical data for OBIZUR supported a favorable benefit/risk determination for the proposed indication of treatment of bleeding episodes in adults with AHA.

These data support the investigation of efficacy and safety of BAX 802 in subjects with CHA with inhibitors undergoing surgical or other invasive procedures.

6.6 Compliance Statement

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

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is to evaluate the efficacy and safety of BAX 802 in males with CHA with inhibitors who are undergoing major or minor elective surgical, dental, or other invasive procedures.

7.2 Primary Objective

The primary objective of the study is to evaluate the perioperative hemostatic efficacy of BAX 802 in male subjects with CHA with inhibitors to hFVIII undergoing major or minor elective surgical, dental, or other invasive procedures as determined by the Global Hemostatic Efficacy Assessment (GHEA) score.

7.3 Secondary Objectives

The secondary objectives of the study are to:

1. To determine the safety of BAX 802 used in the perioperative setting by assessing:
    - The development of and change in titer of anti-pFVIII and anti-hFVIII inhibitory antibodies (binding and neutralizing), and development of binding antibodies to BHK proteins
    - The occurrence of thrombotic events and/or allergic reactions to BAX 802
    - The occurrence of AEs related to BAX 802
    - The occurrence of clinically significant changes in vital signs and routine laboratory parameters related to BAX 802
2. To determine the intra- and postoperative and overall perioperative blood loss at the end of surgery, compared to the estimated volume of expected average and maximum blood loss in a comparable healthy individual as predicted preoperatively by the investigator/surgeon
3. To determine the daily and total weight-adjusted administration of BAX 802 per subject
4. To determine the blood product utilization
5. To determine the occurrence of bleeding episodes during the intra- and postoperative periods and additional need for surgical intervention
6. To evaluate any unrelated bleeding episodes in the postoperative period.

8. STUDY DESIGN

8.1 Brief Summary

This study is a Phase 3, uncontrolled, open-label, single-group, multicenter study to determine the safety and efficacy of BAX 802 in at least 10 surgeries in 10 evaluable male subjects with CHA with inhibitors to hFVIII who are undergoing major or minor elective surgical, dental, or other invasive procedures (at least 5 major surgeries in 5 evaluable subjects).

8.2 Overall Study Design

This study is a Phase 3, prospective, open-label, uncontrolled, multicenter study to evaluate the efficacy and safety of BAX 802 in at least 10 surgeries in 10 evaluable male subjects with CHA with inhibitors to hFVIII who are undergoing major and minor surgical, dental or other invasive procedures. At least 5 of the procedures must be major surgeries in 5 evaluable subjects (see Section 8.2.1).

The dose and frequency of BAX 802 during the preoperative, intraoperative, and postoperative periods should follow a substitution plan provided by the investigator prior to surgery and adjusted based on regular FVIII activity measurements. The regimen will depend on the type of surgery performed and the intensity of the hemostatic challenge.

Elective surgical procedures will prospectively be defined as major or minor by the investigator/surgeon and agreed with the medical director/designee, based on the protocol guidance and definitions and in consideration of each subject's characteristics. Emergency surgeries are not in the scope of this study. Subjects may undergo more than 1 surgery or 2 parallel surgeries, such as bilateral knee replacement. For subjects undergoing multiple surgeries (other than parallel surgeries), the End of Study visit should be completed for the first surgery and then subject needs to be re-screened (Section 10.3) for the next surgery.

The study will be conducted globally and will be divided into 5 periods: Screening, Preoperative, Intraoperative, Postoperative, and End of study (Table 8).

The overall study design is illustrated in Figure 1.

8.2.1 Types of Interventions

Elective procedures will prospectively be defined by the investigator/surgeon as major or minor based on the definitions and examples provided in Section 8.2.1.1 and Section 8.2.1.2 taking into consideration each individual patient's characteristics and agreement with the sponsor.

8.2.1.1 Major Surgeries

Major surgeries include surgeries that require moderate or deep sedation, general anesthesia, or major conduction blockade for patient comfort. This 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 (> 500 mL) or blood loss into a confined anatomical space. Several tooth extractions or extraction of the third molar are generally considered as major. Examples include:

- bone fixation for fracture
- hip and knee replacement (arthroplasty)
- arthrodesis (joint fusion)
- open synovectomy
- osteotomy
- liver biopsy
- pseudotumor removal
- hardware removal (plates, intramedullary nails)

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

8.2.1.2 Minor Surgeries

Minor surgeries include surgeries that can be safely and comfortably performed on a patient who has received local or topical anesthesia, without more than minimal preoperative medication or minimal preoperative medication or minimal intraoperative sedation. The estimated total blood loss should be < 500 mL and the likelihood of complications requiring hospitalization or prolonged hospitalization should be remote. It refers to interventions such as removal of skin lesions, arthroscopy, minor dental procedures or dental extractions. Examples include:

- removal of skin lesions
- 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

- arthroscopy
- 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

8.2.2 Dose Selection Rationale

Background

This is a Phase 3, open label study of the efficacy and safety of B-domain deleted rpFVIII (BAX 802) in the perioperative management of hemostasis in subjects with CHA who have inhibitors and are undergoing surgical or other invasive procedures. The rpFVIII temporarily replaces the inhibited FVIII that is needed for effective hemostasis in CHA patients who have developed inhibitors to hFVIII. The principle of using pFVIII is based on its low cross-reactivity with anti-hFVIII antibodies due to sequence variations between human and pFVIII in the A2 and C2 domains, the main targets of FVIII inhibitors. The rpFVIII concentrate is predicted to have an advantage over human-derived FVIII in CHA patients who have inhibitors since previous studies demonstrated that the antibodies have a median of only 15% cross-reactivity with plasma-derived pFVIII.[18]

Regulatory approval for rpFVIII for the treatment of bleeding episodes in adults with AHA was received for OBIZUR®; per the product label, the initial dose of OBIZUR® is 200 U/kg, with subsequent dosing dependent on the location and severity of bleeding episode, target FVIII levels, and the patient's clinical condition.[17]

Influence of Anti-pFVIII Inhibitor Titer on the Loading Dose

Anti-pFVIII inhibitors are neutralizing antibodies against pFVIII that neutralize the pFVIII, and thereby reduce its hemostasis effect. Anti-pFVIII inhibitors can be quantified in plasma by the Bethesda assay, which measures the ability of the patient's plasma to neutralize exogenous pFVIII when incubated together.

The amount of BAX 802 required to neutralize the anti-pFVIII activity is factored in. A BU is defined as the amount of anti-pFVIII inhibitor in a plasma sample which will neutralize 50% of 1 unit of BAX 802 in normal plasma after 2 hour incubation at 37°C.

Only the inhibitor that is distributed in the plasma volume (PV) is initially available to neutralize the infused FVIII; PV is calculated using the following formula:

PV = Blood Volume x (1 – [hematocrit{Hct}%/100])

Normal blood volume is approximately 80 mL/kg for adults.

Therefore, PV = 80 x (1 – [Hct%/100]).

One BU of anti-pFVIII inhibitor will neutralize 50% of 1 unit of BAX 802; therefore, it is assumed that 0.5 U FVIII will be required for each 1 BU of inhibitor. The amount of BAX 802 required to neutralize the anti-pFVIII activity can be estimated using the following:

Body weight x 80(1 - [Hct%/100]) x 0.5 x anti-pFVIII inhibitor titer (BU) =
body weight x 40(1-[Hct%/100]) x anti-pFVIII inhibitor titer (BU).

Proposed Dosing Regimen of BAX 802 in Study BAX 802 Surgery

This regimen for loading dose of BAX 802 proposed for Study BAX 802 Surgery takes into account the titer of anti-pFVIII inhibitors. The dosing scheme to be used in Study BAX 802 Surgery is presented in Section 8.7.3.3.

The loading dose of BAX 802 for a CHA subject with inhibitors undergoing major surgery is calculated using the following formula:

80 U/kg + body weight x 40(1-[Hct%/100]) x anti-pFVIII inhibitor titer (BU)

For example, for a 70 kg subject undergoing major surgery and having hematocrit 45% and anti-pFVIII inhibitor titer 3 BU, the loading dose of BAX 802 will is calculated as follows:

80 (70) + 70 x 40(1-[45/100]) x 3 = 10,220 U

This dosing scheme should reasonably predict the loading dose before surgery that will provide sufficient FVIII levels needed for effective hemostasis.

Subsequent doses, dosing frequency, and duration of treatment will be based on clinical judgment and measured FVIII levels achieved, and will require empirically based adjustments until hemostasis is achieved (Table 5).

This dosing algorithm is essentially equivalent to that proposed by Kasper (2004) when using FVIII in the treatment of patients with low titer inhibitors.[19]

8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study will be approximately 20 months from study initiation (ie, first subject enrolled) to study completion (ie, last subject, last visit). The recruitment period is expected to be 13 to 16 months.

The duration of subject participation depends on the nature of the invasive procedure: it will run from the signing of the informed consent until completion of the End of Study Visit up to 6 weeks post-surgery (surgery = Day 0), unless prematurely discontinued. Study completion is defined by the End of Study Visit after discharge.

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

The primary outcome measure is the GHEA score (Table 1), which is composed of 3 individual ratings:

- Assessment of intraoperative hemostatic efficacy of BAX 802 performed by the operating surgeon (see Table 2)
- Assessment of postoperative hemostatic efficacy of BAX 802 at postoperative Day 1 (approximately 24 hours after surgery) performed by the operating surgeon (see Table 3)
- Assessment of overall perioperative hemostatic efficacy of BAX 802 at Day 14 or discharge (whichever is earlier), performed by the investigator (see Table 4)

The scores of each of the 3 individual ratings described above, will be added together to form a GHEA score according to Table 1. For a GHEA score of 7 to be rated "excellent" no individual assessment score should be less than 2 (ie, one individual assessment score must be 3 and the other 2 individual assessment scores must be 2). The only other option to achieve a GHEA score of 7 is for 2 individual assessment scores of 3 and one individual assessment score of 1. Although this GHEA score will not qualify for a rating of "excellent," the GHEA score will satisfy the definition of "good," (with no individual assessment score less than 1). All possible combinations of the individual assessment scores and their related ratings are provided in Supplement Section 20.5. Missing scores will be counted as 0.

The assessment of primary outcome measure (GHEA score) should only account for the blood loss related to the surgery and exclude any blood loss which is considered as unrelated bleeding (defined as any bleeding occurring at a different anatomical site than the surgery site during the postoperative period, see Section 11.2.5).

Table 1: Global Hemostatic Efficacy Assessment (GHEA)	
Assessment	**GHEA Score**
Excellent	7[a] to 9 (with no category scored < 2)
Good	5 to 7[a] (with no category scored < 1)
Fair	3 to 4 (with no category scored < 1)
None	0 to 2 (or at least one category scored 0)

[a] For a GHEA score of 7 to be rated "excellent" (with no individual assessment scores less than 2), at least 1 individual assessment score must be 3 and the other 2 individual assessment scores must be at least 2; otherwise a score of 7 is rated "good".

Table 2: Intraoperative Efficacy Assessment Scale		
A	*At the time of discharge from the OR, the operating surgeon will assess the intraoperative hemostatic efficacy*	
Rating	**Criteria**	**Score**
Excellent	Intraoperative blood loss was less than or equal to that expected for the type of procedure performed in a non-hemophilic population (≤ 100%)	3
Good	Intraoperative blood loss was up to 50% more than expected for the type of procedure performed in a non-hemophilic population (101 to 150%)	2
Fair	Intraoperative blood loss was more than 50% of that expected for the type of procedure performed in a non-hemophilic population (> 150%)	1
None	Uncontrolled hemorrhage that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy	0

Table 3: Postoperative Efficacy Assessment Scale (Postoperative Day 1)		
B	*On postoperative Day 1, the operating surgeon will assess the postoperative hemostatic efficacy by the operating surgeon*	
Rating	**Criteria**	**Score**
Excellent	Postoperative blood loss was less than or equal to (≤ 100%) that expected for the type of procedure performed in a non-hemophilic population	3
Good	Postoperative blood loss was up to 50% more (101% to 150%) than expected for the type of procedure performed in a non-hemophilic population	2
Fair	Postoperative blood loss was more than 50% (> 150%) of that expected for the type of procedure performed in a non-hemophilic population	1
None	Significant postoperative bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy	0

Table 4: Overall Perioperative Efficacy Assessment Scale (Day 14)		
C	*At Day 14 or discharge (whichever is earlier), a hematologist will assess the postoperative efficacy*	
Rating	**Criteria**	**Score**
Excellent	Overall perioperative blood loss was less than or equal to (≤ 100%) that expected for the type of procedure performed in a non-hemophilic population, Required blood components for transfusions were less than or similar to that expected in non-hemophilic population	3
Good	Overall perioperative blood loss was up to 50% more (101% to 150%) than expected for the type of procedure performed in a non-hemophilic population Required blood components for transfusions were less than or similar to that expected in non-hemophilic population	2
Fair	Overall perioperative blood loss was more than 50% of that expected for the type of procedure performed in a non-hemophilic population (> 150%) Required blood components transfusions were greater than that expected in non-hemophilic population	1
None	Significant overall 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 that expected in non-hemophilic population	0

8.4.2 Secondary Outcome Measures

8.4.2.1 Efficacy

1. Blood loss compared to the estimated volume of expected average blood loss and expected maximum blood loss in a comparable healthy individual as predicted preoperatively by the investigator/surgeon at the following time points:
    - Intraoperative, at the end of surgery
    - Postoperative Day 1, approximately 24 hours after surgery
    - Overall perioperative Day 14 or discharge (whichever is earlier)
2. Daily and total weight-adjusted administration of BAX 802 per subject
3. Volume of blood, red blood cells, platelets, and other blood products transfused
4. Occurrence of bleeding episodes during the intra- and postoperative periods and additional need for surgical intervention
5. Efficacy of the treatment of unrelated bleeding episodes in the postoperative period.

8.4.2.2 Safety

1. Development of, and changes to, the titer of inhibitory and binding antibodies to rpFVIII
2. Development of, and changes to, the titer of inhibitory and binding antibodies to hFVIII
3. Development of binding antibodies to BHK proteins
4. Occurrence of thrombotic events
5. Incidence of severe allergic reactions (eg, anaphylaxis)
6. Incidence of other IP-related AEs
7. Incidence of clinically significant changes in vital signs and routine laboratory parameters (hematology, clinical chemistry)

8.5 Randomization and Blinding

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

8.6 Study Stopping Rules

The study will be halted (enrollment stopped), pending further review by the internal Safety Monitoring Committee (ISMC) and sponsor, if 1 or more of the following criteria are met:

1. Two or more subjects develop a severe anaphylactoid reaction or any other serious adverse event (SAE) related to BAX 802 that would not be expected with a currently licensed rpFVIII product (OBIZUR®)
2. Other AEs that are deemed to pose unacceptable risks to subjects.

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

1. The sponsor decides to terminate the study based upon ISMC recommendation or its own assessment of safety
2. The sponsor decides to terminate the study at any time for administrative reasons.

8.7 Investigational Product(s)

BAX 802 will be supplied as white lyophilized powder in 3 mL glass vials containing nominally 500 units per vial for reconstitution with 1.0 mL sterile water for injection.

8.7.1 Packaging, Labeling, and Storage

BAX 802 will be supplied in a lyophilized form. For specific instructions for reconstitution, please refer to the Study Manual. A sufficient quantity of BAX 802 will be supplied to each study site, as well as an acknowledgement of receipt form.

The core label texts for all packaging units will be translated or adjusted, to be in compliance with applicable regulatory requirements, national laws in force and in accordance with the local languages. Minimally each vial will bear a label with the following information:

- Sponsor name
- Study number
- Pharmaceutical dosage form
- Route of administration
- Name of IMP and actual quantity of dose units
- Batch number
- Space on which to record the subject number
- The statement 'For clinical trial use only' or 'Caution: new drug limited by Federal Law to investigational use' or 'To be used only by a qualified investigator', as appropriate
- Name, address and telephone number of the Sponsor, Contract Research Organization (CRO) or investigator, if appropriate
- Storage conditions
- Expiry or manufacturing date, as appropriate

The investigator or designee will only dispense BAX 802 to subjects included in this study.

8.7.2 Reconstitution and Administration

The reconstitution procedures for BAX 802 are detailed in the Pharmacy Manual. Reconstituted BAX 802 should be kept and administered at room temperature and must be administered within 3 hours of reconstitution.

BAX 802 will be administered as an intravenous infusion per the dosing schema for major and minor surgeries (Table 5).

8.7.3 Description of Treatment

8.7.3.1 FVIII Maintenance Plan

Based on the category (minor or major) and type of surgery, the investigator must outline the expected FVIII maintenance plan with target peak and trough levels covering the surgical, dental or invasive procedure until expected wound healing. The FVIII maintenance plan will be provided to the medical director/designee to ensure that the recommendations regarding FVIII target levels as provided in the protocol are followed. Each FVIII maintenance plan for major surgeries requires prior approval of the medical director. The FVIII levels measured intra/postoperatively will be compared with the FVIII maintenance plan. Slight deviations from the predefined substitution plan are allowed based on investigators clinical judgment and available laboratory FVIII data.

It is recommended that the turnaround time for FVIII activity results from the local laboratories are ≤ 2 hours so that dosing decisions could be made and subjects are dosed adequately.

8.7.3.2 Perioperative Dosing

Adjustments to the dose and frequency of BAX 802 dosing during the intra- and postoperative period should follow the maintenance plan provided by the investigator prior to surgery. Adjustments must be based on regular FVIII activity measurements determined at pre- and post-dosing of BAX 802 and will depend on the type of the surgery performed and the intensity of the hemostatic challenge.

8.7.3.3 Dosing Schedule and Requirements

8.7.3.3.1 General

As described in Section 8.2.2, the loading dose will be calculated according to the following formula:

Loading Dose of BAX 802:

- Major Surgery: 80 U/kg + body weight (kg) x 40(1-[Hct%/100]) x anti-pFVIII inhibitor titer (BU), administered approximately 1 to 2 hours prior to the surgery
- Minor Surgery: 50 U/kg + body weight (kg) x 40(1-[Hct%/100]) x anti-pFVIII inhibitor titer (BU), administered approximately 1 to 2 hours prior to the surgery

The loading dose of BAX 802 for a CHA subject with inhibitors undergoing major surgery is calculated using the following formula:

80 U/kg + body weight (kg) x 40(1-[Hct%/100]) x anti-pFVIII inhibitor titer (BU)

For example, for a 70 kg subject undergoing major surgery and having hematocrit 45% and anti-pFVIII inhibitor titer 3 BU, the loading dose of BAX 802 will be calculated as follows:

80 (70) + 70 x 40(1-[45/100]) x 3 = 10,220 U

Subsequent doses, dosing frequency, and duration of treatment will be based on the clinical judgment and measured FVIII levels achieved, and will require empirically based adjustments until hemostasis is achieved based on the following calculation (Table 5):

Required dose (U) =
[body weight (kg) x desired FVIII rise (U/dL or % of normal)]/1.2 (U/kg per U/dL).

Table 5: Dosing for Perioperative Management

Type of Surgery	Recommended FVIII Level (% of normal or U/dL)	Loading Dose	Subsequent Dose
Major (see Section 8.2.1.1)	**Prior to surgery:** ≥ 80% **Postoperative up to 72 hours (if not yet discharged):** ≥ 80% **Postoperative Day 4 – Day 7 (if not yet discharged):** ≥ 50% (if not yet discharged) **Postoperative Day 8 to discharge (if not yet discharged):** it is recommended that the FVIII levels do not fall below 30% (left to the discretion of the investigator depending on the postoperative course)	80 U/kg + body weight (kg) x 40(1-[Hct%/100]) x anti-pFVIII inhibitor titer (BU)[1], administered approximately 1 to 2 hours prior to the surgery	Titrate subsequent doses to maintain recommended FVIII trough levels and individual clinical response using following formula: Required dose (U) = [body weight (kg) x desired FVIII rise (U/dL or % of normal)]/1.2 (U/kg per U/dL)
Minor (see Section 8.2.1.2)	**Prior to surgery:** ≥ 50% **Postoperative up to 72 hours (if not yet discharged):** ≥ 50% **Postoperative Day 4 to discharge (if not yet discharged):** it is recommended that the FVIII levels do not fall below 30% (left to the discretion of the investigator depending on the postoperative course)	50 U/kg + body weight (kg) x 40(1-[Hct%/100]) x anti-pFVIII inhibitor titer (BU)[1], administered approximately 1 to 2 hours prior to the surgery	

[1] Anti-pFVIII inhibitor titer and hematocrit information available from screening lab result will be used.
Note: It is recommended that the plasma levels of FVIII do not exceed 200% of normal.

If at any time during the study, a subject does not respond to BAX 802 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. In the event of unexplained, excessive bleeding, the subject will be treated by whatever means necessary until adequate hemostasis is achieved. If other rescue medications become necessary, the subject will subsequently be withdrawn from this BAX 802 surgery study. Adverse events and the details of concomitant medication and blood product use coincident with the treatment of all unanticipated bleeding will be recorded. The use of adjunct antifibrinolytic therapy (such as tranexamic acid) is allowed if clinically indicated by the investigator and/or according to the standard of care of the subject's institution.

8.7.3.3.2 Preoperative and Loading Dose

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

The initial loading dose will be administered within 60 to 120 minutes prior to surgery (prior to incision/intubation).

In case of major surgery, FVIII target level is ≥ 80% for major surgeries/procedures and ≥ 50% for minor surgeries/procedures.

It is recommended that the surgery starts after FVIII levels have achieved target levels. If FVIII activity post loading dose is close to the target level, a supplement dose of BAX 802 should be administered without further delaying the surgery. If FVIII activity post loading dose is not close to the target level, a supplement dose of BAX 802 should be administered and surgery delayed until FVIII levels have achieved target levels or are in close range.

ALL subsequent dosing of BAX 802 should be preceded by measurement of residual FVIII levels and dose adjustments must be based on the most recent residual FVIII activity levels.

Note: It is recommended that the plasma levels of FVIII do not exceed 200%.

Note: Dose adjustments should not be based on activated partial thromboplastin time (aPTT) values.

8.7.3.3.3 Postoperative Dosing

Major Surgery

After the initial loading dose, an optional re-dosing 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:

- **FVIII activity level should be determined immediately after the procedure/surgery has been completed, with dose adjustments as necessary.**
- **FVIII activity level should also be determined within 4 to 6 hours following major surgery, with dose adjustments as necessary.**
- **Following this, FVIII activity level should be determined at least every 12 hours till 48 hours postoperative period (if not discharged yet), with dose adjustments as necessary.**
- **Beginning on postoperative Day 3 (through discharge), subjects will have FVIII level measurement at least once per day in order to assess the adequacy of BAX 802 therapy during the postoperative period. For consistency, it is recommended that the daily blood draws are performed at the same time of the day, such as morning blood draws.**

More frequent monitoring of FVIII activity is advised in subjects who have baseline anti-pFVIII inhibitor titers of >5 BU.

ALL subsequent dosing of BAX 802 must be preceded by measurement of residual FVIII levels pre-dose and FVIII level measurement 30 ±5 minutes post-dosing.

It is recommended that the FVIII trough levels are within the range targeted for major surgery as per Table 5. Dosing adjustments based on aPTT values are not allowed.

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

At a minimum, a blood sample for FVIII determination must be drawn prior to any supplemental unscheduled FVIII infusion and 30 ±5 minutes post-dosing.

Minor Surgery

After the initial loading dose, an optional re-dosing 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:

- **FVIII activity level should be determined immediately after the procedure/surgery has been completed, with dose adjustments as necessary.**
- **FVIII activity level should also be determined within 4 to 6 hours following minor surgery, with dose adjustments as necessary on the day of surgery.**
- **Following this, FVIII activity level should be determined at least every 12 hours till 48 hours postoperative period (if not discharged yet), with dose adjustments as necessary.**
- **In case the subject is hospitalized for more than 24 hours, daily pre- and post-infusion FVIII level determinations as described for major surgery have to be performed and the dose adjusted according to the residual FVIII levels.**

More frequent monitoring of FVIII activity is advised in subjects who have baseline anti-pFVIII inhibitor titers of > 5 BU.

ALL subsequent dosing of BAX 802 must be preceded by measurement of residual FVIII levels and the dose adjusted as needed. Dosing adjustments based on aPTT values are not allowed.

It is recommended that the FVIII trough levels are within the range targeted for minor surgery as per Table 5.

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

8.7.3.3.4 Dosing for Unrelated Bleeding Episodes During the Postoperative Period

Unrelated bleeding episode is defined in Section 11.2.5.

The BAX 802 dosing regimen for treatment of these bleeding episodes will be based on the guidelines in Table 6. These guidelines may be adjusted by the investigator based upon his or her clinical judgment.

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

Repeat infusions of BAX 802 can be administered to treat these bleeding episodes, as per investigator's discretion.

When bleeding is controlled, additional infusions of BAX 802 to maintain hemostasis are permitted, if required. Infusions given to treat and control the unrelated bleeding episode should be documented in the eCRF.

For a detailed description of bleeding episodes into different sites see Supplement 20.6.

Table 6: BAX 802 Treatment Guidelines for Unrelated Bleeding Episodes		
Type of Bleeding Episode	**Recommended FVIII Level (%)**	**BAX 802 Dose**
Minor Early hemarthrosis, mild muscle bleeding, or mild oral bleeding, including, epistaxis	20% to 40%	Required dose (U) = [body weight (kg) x desired FVIII rise[1] (U/dL or % of normal)]/1.2 (U/kg per U/dL) Titrate subsequent doses to maintain recommended FVIII trough levels and individual clinical response until the bleeding resolves.
Moderate Moderate bleeding into muscles, bleeding into the oral cavity, definite hemarthrosis, and known trauma	30% to 60%	
Major Significant gastrointestinal bleeding, intracranial, intra-abdominal, or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces or iliopsoas sheath, fractures, head trauma	60% to 100%	

[1] If the most recent residual FVIII activity level is from the measurement performed ≤ 4 hours of the bleeding episode, use this value to calculate desired FVIII rise. If the most recent residual FVIII activity level is from the measurement performed > 4 hours of the bleeding episode, the desired FVIII rise should be equivalent to the recommended FVIII level for that type of bleeding episode (as described in the column to the left).
Note: It is recommended that the plasma levels of FVIII do not exceed 200% of normal.

8.7.4 Thrombosis Prophylaxis and Topical Hemostatics

Commercially available gelatin sponges, topical thrombin, fibrin sealants, absorbable collagen preparations or anti-fibrinolytics (eg, tranexamic acid, ε-amino caproic acid) may be used according to each institution's standard of care. Details, including the dose, of all adjunctive hemostatic medication used will be recorded in the eCRFs designed for this study and the reason for use given.

Thrombosis prophylaxis can be administered at the discretion of the investigator according to the standard of care of each institution and recorded into the respective eCRF. Thrombosis prophylaxis should preferably consist of mechanical measures such as intermittent pneumatic compression (IPC), compression stockings and early mobilization. Pharmacologic thrombosis prophylaxis such as low molecular weight heparin (LMWH) may be considered for certain surgical interventions such as major orthopedic surgery after careful evaluation by the investigator of the potential risks and benefits.

8.7.5 Investigational Product Accountability

The investigator will ensure that the IP(s) 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(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. IP(s) must be dispensed only at the study site or other suitable location (eg, infusion center; home, as applicable per study design). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) 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(s) 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, 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.

No data will be entered directly onto the case report form (CRF).

For additional information on study documentation and CRFs, see Section 17.2.

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 ≥ 18 to ≤ 65 years old at the time of screening
2. Subject has provided signed informed consent
3. Subject has severe (FVIII level < 1%) or moderately severe (FVIII level ≤ 2%) CHA with inhibitors to human FVIII, as tested at screening at the central laboratory
4. Subject requires elective surgery or other invasive procedures
5. Subject is not currently receiving or has received (< 30 days) ITI therapy
6. Subject has a Karnofsky performance score of ≥ 60
7. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm3 at screening
8. Subject is hepatitis C virus negative (HCV-) by antibody or polymerase chain reaction (PCR) testing; or HCV+ with chronic stable hepatitis disease
9. Subject is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

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

1. The subject requires emergency surgery
2. The subject's weight is < 35 kg or > 120 kg
3. Clinically symptomatic liver disease (eg, ≥ 5 X upper limit of normal alanine aminotransferase [ALT], as confirmed by central laboratory at screening, clinical evidence of portal hypertension, severe hypoalbuminemia or a documented prothrombin time/international normalized ratio (PT/INR) > 1.5)
4. Clinically symptomatic renal disease (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening
5. Anti-porcine inhibitor > 10 BU prior to surgery
6. Platelet count < 100,000/μL
7. Subject has another active coagulation disorder other than hemophilia A, as per the medical history

8. Planned use of α-interferon with or without ribavarin for HCV infected patients or planned use of a protease inhibitor for HIV infected patients. Patients currently taking any of these medications for ≥ 30 days are eligible
9. Known hypersensitivity to rpFVIII, or hamster or murine proteins
10. Subject has been exposed to an IP 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
11. Unable to tolerate quantity of blood to be drawn for protocol procedures
12. Subject is a family member or employee of the investigator.

9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (ie, reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) are described in Section 10.7, Section 20.3, and Section 20.4.

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

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

- AEs/SAEs that in the investigator or sponsor opinion, poses an unacceptable risk for continued dosing in the subject
- The subject is determined by the sponsor or investigator to be noncompliant with administration of IP, despite evidence of retraining of the subject. The subject will be discontinued from further participation in the study
- Participation in another clinical study involving an IP during the course of the study
- The subject experiences a severe anaphylactic reaction
- The subject had uncontrolled hemorrhage that was the result of inadequate therapeutic response despite proper dosing of rpFVIII, necessitating rescue therapy with bypassing agents.

10. STUDY PROCEDURES

10.1 Informed Consent

Any patient who provides informed consent (ie, signs and dates the informed consent form and assent form, if applicable) is considered a subject in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (241502) to be provided by the sponsor, 2-digit number study site number (eg, 02) to be provided by the sponsor, and 3-digit subject number (eg, 003) reflecting the order of providing informed consent. For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 241502-02003. 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 a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure.

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

Subjects who fail screening due to a single laboratory test result that does not meet eligibility criteria may have that laboratory test repeated at the discretion of the investigator. This will include a repeat of only the failed assessment; complete re-screening will not be necessary. In these cases, a new SIC is not required; the subject will maintain their original SIC. The repeat of a screening assessment is allowed once. A repeat assessment must take place within 42 days of the initial screening for any subject requiring repeat of a screening assessment. If this timeframe is exceeded, then all screening assessments must be repeated and the subject assigned a new SIC. Exemptions are possible for administrative reasons and have to be approved by the sponsor. Subjects with an inadequate interval between screening and prior IP drug (other than BAX 802) administration or prior participation in a drug or device study (ie, 30 days), may be re-screened only once and only when the required interval is reached.

The screening assessment should be performed within 45 days prior to the planned elective surgery.

The overall study design is illustrated in Supplement Figure 1. Details on the procedures to be performed at each study visit, including screening, can be found in Supplement 20.3 and Supplement 20.4.

10.4 Study Periods

The study will be divided into 5 periods:

1. Screening
2. Preoperative
3. Intraoperative
4. Postoperative
5. End of study

A detailed description of study procedures per study period is provided in Supplement 20.1.

10.4.1 Discharge/End of Study Visit

Discharge Visit will be performed when the subject is discharged and the End of Study Visit will be performed 42 to 49 days following the completion of the surgical procedure. In cases where the Discharge Visit would occur within 3 days of either the Day 14 or the End of Study visit, the respective visits will be done as a single visit.

10.4.2 Optional Antibody Testing Visit

Whenever feasible, a visit will be performed between 7 to 14 days after the subject is discharged. Study procedures will be performed as per Table 9 and blood samples will be collected for antibody testings and other tests as per Table 10. This visit is optional.

10.5 Medications and Non-Drug Therapies

The following medications are **not** permitted:

Medications:

- Hemophilia inhibitor bypassing therapy (recombinant factor VIIa [NovoSeven] within 3 hours or aPCC [FEIBA)] within 6 hours prior to initial BAX 802 administration) unless used as a rescue medication (Section 10.5) after failure/study withdrawal
- Hemophilia medication other than BAX 802 at any time during the study.

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

The following medications and non-drug therapies are permitted within 30 days before study entry and during the course of the study:

Medications:

- The management of a serious thrombo-embolic event may require anticoagulant medication and this may need to be administered concurrent with the use of BAX 802 to ensure that a re-bleed or continuing severe hemorrhage does not occur on withdrawal of BAX 802 (see Section 10.6). In such instances the Sponsor's medical monitor should be consulted.
- Any medications deemed necessary by the subject's physician to treat or prevent any medical condition (with the exception of those listed as not permitted)
- Any over-the-counter medication used by the subject to treat symptoms or signs of any medical condition
- Supplemental vitamins, minerals

Non-drug therapies:

- Any non-drug therapy (eg, physiotherapy) deemed necessary by the subject's physician to treat or prevent any medical condition

10.6 Rescue Medications

Bypassing agents (FEIBA or NovoSeven) can be used as a rescue medication if expected plasma FVIII activity levels are not attained or if bleeding is not controlled despite proper dosing of BAX 802 during the intra- or postoperative period of the study. At least 2 doses of BAX 802 needs to be administered before the subject is considered to be a treatment failure and switched to the rescue medication.

10.7 Subject Completion/Discontinuation

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

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation 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), 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 20.3 and Supplement 20.4.

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.

10.8 Procedures for Monitoring Subject Compliance

Subject compliance with the procedures and treatment(s) outlined above will be monitored by direct review of the subject's source data at the sites and evaluated against the protocol requirements. Additionally, electronic edit checks will be performed on all protocol-specified procedures and treatment data that are collected to ensure quality and accuracy. Deviations from the protocol-specified procedures and treatments will be noted in the final study report.

All study procedures are to be performed under the direct supervision of the investigator/a licensed healthcare professional at the study site, and thus, no separate procedures will be used to monitor subject compliance.

11. ASSESSMENT OF EFFICACY

11.1 Primary Efficacy Endpoint: Global Hemostatic Efficacy Assessment Score

The primary outcome measure is the GHEA, which is composed of 3 individual categorical ratings which will be added together to form a GHEA score according to Table 1 (see Section 8.4.1).

11.2 Secondary Efficacy Endpoints

11.2.1 Blood Loss

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

Prior to the surgery, the surgeon/investigator will predict the estimated volume (in 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 end of study visit).

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

11.2.2 Blood Transfusions

The type and volume (in mL) of blood products will be recorded from initiation of the intervention to postoperative Day 14 or discharge (whichever is earlier). Furthermore, also salvage of blood obtained from autologous transfusion systems, eg, cell savers, will be recorded. In addition, the type and volume of fluid replacement and volume expanders will be recorded as concomitant medication (eg, volume of salvaged blood, red blood cells, platelets and other blood products transfused).

11.2.3 Bleeding Episodes

Any clinically relevant bleeding episodes (as assessed by the investigator), as well as the need for any further surgical interventions, will be recorded. Study subjects will be closely monitored for the occurrence of bleeding episodes during the entire intra- and postoperative period, until the time of discharge or until the subject resumes his previous treatment regimen, whichever is later.

Any subject who is deemed to have excessive, unexplained bleeding will have blood drawn for measurement of FVIII levels. Treatment of such events should be performed as per standard of care at the institution.

11.2.4 BAX 802 Administration

The daily and total weight-adjusted administration of BAX 802 per subject will be recorded.

11.2.5 Hemostatic Efficacy Rating for Treatment of Unrelated Bleeding Episodes

An unrelated bleeding episode is defined as any bleeding occurring at a different anatomical site than the surgery site during the postoperative period.

- If these unrelated bleeding episodes occur during the subject's stay in hospital, it is recommended that subjects are treated with BAX 802. BAX 802 will be dosed as per the most recent residual FVIII activity level and clinical judgment using the dosing regimen provided in Table 6 [Required dose = body weight (kg) x desired FVIII rise (U/dL or % of normal)]/1.2 (U/kg per U/dL)]. All subsequent dosing of BAX 802 should be preceded by measurement of residual FVIII levels and dose adjustments must be based on the most recent residual FVIII activity levels.
- If these unrelated bleeding episodes occur after the subject has been discharged, subjects will be treated with standard of care, as per investigator's discretion.

If subject is treated with BAX 802 for unrelated bleeding episodes, the subject will rate the severity (minor, moderate, or major) of the bleeding episode and will rate the overall treatment response at 24 ±2 hours after the initiation of treatment and at the resolution of bleed (if not resolved within 24 hours) using a 4-point efficacy rating scale (Table 7). 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 1 or more than 1 location, consider the injury-related symptoms when performing the efficacy rating 24 hours after initiating treatment and at resolution of bleed.

As per Table 5, multiple infusions of BAX 802 may be administered for the treatment of a bleeding episode. The overall response to all infusions combined is the rating that will be recorded at resolution of bleed.

Table 7: Efficacy Rating Scale for Treatment of Unrelated Bleeding Episodes	
Excellent	Full relief of pain and/or 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.

11.3 Factor VIII Activity

Blood will be obtained for assessment of FVIII activity at screening (tests to be performed at the **central laboratory**). Results from **local laboratory** will be used to make any dosing decisions.

Blood will be obtained for assessment of FVIII activity for patient management purposes at the following timepoints (tests to be performed at the **local laboratory**, with additional back-up samples to be tested in 1 batch at the **central laboratory**):

- Within 30 minutes prior to the administration of the initial loading dose preoperatively and 30 ±5 minutes post-infusion. If re-dosing with BAX 802 is required to obtain the required FVIII levels, an additional blood sample needs to be drawn 30 ±5 minutes following the re-dosing with BAX 802.
- Postoperatively until day of discharge from the investigative site: daily within 30 minutes prior to the infusion of BAX 802 and 30 ±5 minutes post-infusion. Pre- and post-dosing blood draws for FVIII activity level determination should also be performed for each BAX 802 administration.
- FVIII activity will also be assessed if the subject has excessive, unexplained bleeding at any time intra-or postoperatively, or whenever deemed necessary according to the institution's standard of care.

11.3.1 Blood Sampling and Processing for FVIII Analysis

At each blood sampling time point whole blood will be collected in blood sampling tubes will be collected in S-Monovette® tubes (Sarstedt, Nümbrecht, Germany) containing 3.2% trisodium citrate, or equivalent blood drawing equipment (eg, Vacutainer tubes), and immediately mixed. The citrated whole blood samples will be capped and transported at room temperature (ie, 20 to 25°C) to the local clinical laboratory for centrifugation, processing, and storage. Monovettes must be kept in an upright position at all times to avoid leakage.

All samples taken through 6 hours post-dosing will be collected from an extremity other than that used for the infusion of study product. Thereafter, either extremity may be used to obtain samples.

If the subject has a central 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 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 sample.

All citrated plasma samples will be stored and shipped to the central laboratory at ≤ -70°C for testing.

All back-up samples collected during the perioperative period will be shipped to the central laboratory as soon as possible in 1 batch and analyzed, as needed.

Blood samples will be analyzed for FVIII activity (1-stage clotting assay and the chromogenic assay) at the central laboratory. The 1-stage FVIII activity assay will serve as the primary assay; the chromogenic assay of FVIII activity will be used to provide supportive data. Local laboratories are expected to use a 1-stage clotting assay.

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 1 or more of the following criteria:

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

- Thromboembolic events (eg, stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism).

Planned hospitalization for any study procedures as per the protocol will not be considered as 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 (RSI). "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 product, but are not specifically mentioned as occurring with the particular product under investigation. The expectedness of AEs will be determined by the sponsor using the Company core Data Sheet for OBIZUR as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.

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 are collected under other study endpoints and thus are not reportable on the AE CRF, nor will they be included in the analysis of AEs:

Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be assessed as part of the efficacy assessments. However, the investigator may decide that the event is an AE if the event also would have occurred in a normal patient under the same circumstances. If a bleeding episode was caused by an injury, the injury will be reported as an AE.

All other/Each AE from the first IP exposure until study completion or 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 resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (ie, the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

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

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the provided SAE Report 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, 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.

12.1.2.3 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Table 9) and Section 12.1.

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

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the IP, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported via the Electronic Data Capture (EDC) system by completing the relevant electronic Case Report Form (eCRF) page(s) in English. For instances in which the EDC may become unavailable, SAEs must be reported using the back-up paper SAE Report Form to meet the 24 hour timeline requirement (contacts and instructions to be provided in separate documentation).

Once the EDC becomes available, the site must enter all SAE data as reported on the back-up paper SAE report form on the applicable eCRF pages.

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

- Protocol Number
- Subject identification number and demographics (gender, age at onset of event and/or date of birth)
- IP exposure
- Medical Term for Event (Diagnosis preferably)
- Description of the (S)AE, including:
  - Date of onset
  - (S)AE treatment (drug, dose, route of administration)
  - Causal relationship by the Investigator
  - Measures taken (ie, action taken regarding IP in direct relationship to the AE)
- Seriousness criteria (ie, death, life-threatening, or other criterion)
- Cause of death
- Autopsy findings (if available)
- Name, address, fax number, email, and telephone number of the reporting
- Investigator (for paper SAE Report Forms)

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(s) and relevant competent authority(s) are notified of the urgent safety measures 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 AE CRF (and SAE Report Form if eCRF is not available). These events will not be considered as SAEs and will not be included in the analysis of SAEs.

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

- Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be assessed as part of the efficacy assessments. If a bleeding episode was caused by an injury, the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (eg, abrasion of skin). Therefore, any hemophilia-related event (eg, hemarthrosis [presenting as swelling, pain, and decreased range of motion], bruising, hemorrhages, or pain at bleeding episode site) will not be reported as AEs. However, the Investigator may decide that the event is an AE if the event also would have occurred in a normal patient under the same circumstances.

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.

Medical history will include the collection of hemophilia history, bleeding episode history, and history of aPCC or rFVIIA usage for 12 months prior to screening. Relevant medical and surgical history and all medications taken 3 months prior to screening will also be collected.

All medications taken and non-drug therapies received within 3 months before providing informed consent until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Table 9), 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

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

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) and platelet counts.

Clinical chemistry and hematology assessments will be performed on EDTA-anticoagulated serum and whole blood, respectively, at the central laboratory. The frequency of blood draws for clinical and hematology assessments is provided in Table 10.

Details of blood sampling volumes are presented in the laboratory manual and master ICF.

12.7.1 Hematology, Clinical Chemistry, and Urinalysis

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) and platelet counts.

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

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening/baseline, all study visits (ie, pre- and perioperatively and daily while the patient is at the study site), and at study completion/termination. Hematology and clinical chemistry assessments will be performed on EDTA-anticoagulated whole blood and serum, respectively, at the central or local laboratory.

The urinalysis panel will consist of pH, protein, ketones, glucose, bilirubin, blood, urobilinogen, specific gravity by dipstick and microscopy if any findings are abnormal.

Urine will be obtained for assessment of urinalysis parameters at screening and at study completion/termination.

12.7.2 Viral Serology

Viral serology testing will include HIV-1 and HIV-2 antibody, HAV (immunoglobulin M [IgM] and total antibodies), hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), HCV antibody, and parvovirus B19 (IgM and immunoglobulin G [IgG] antibodies). The HIV and HCV titer will be confirmed by PCR for all subjects reported as HIV and HCV positive. All viral serology assessments will be performed at screening. Any positive HBsAg test will be repeated using a new blood sample.

12.7.3 Immunogenicity

Immunogenicity assessments will include anti-pFVIII and hFVIII binding and inhibitory antibodies and anti-BHK binding antibodies.

Blood samples will be collected for the assay of anti-pFVIII and hFVIII binding and inhibitory antibodies and anti-BHK binding antibodies at the times indicated in Table 9 and Table 10.

All FVIII assays related to study subject management decisions by the investigator will be performed at the investigator's local laboratory.

A central reference laboratory will perform assays (anti-pFVIII, anti-hFVIII, and anti-BHK) on samples taken at the Screening, Day 14 or discharge (whichever is earlier), and End of Study Visits.

Binding antibodies to pFVIII, hFVIII, and BHK, will be measured using ELISA. The assessment of inhibitory antibodies to porcine and hFVIII will be determined using a Bethesda assay (with the Nijmegen modification if possible). Further details on blood collection, tube preparation and shipment will be provided in the Study Manual.

12.7.4 Assessment of Laboratory Values

12.7.4.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each laboratory value will be recorded on the CRF. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes an 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.

12.7.5 Backup Samples and Biobanking

Backup samples taken and stored short-term may be used for re-testing, follow-up of an AE(s) or other test results (such as FVIII activity and antibody testing), and/or assay development.

After study testing is completed, the remaining samples may be stored in a coded form for no more than 2 years after final study report completion and then the samples will subsequently be destroyed.

For this study, no samples will be taken or stored long-term in a biobank for future analyses.

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) measured once at screening, and weight (lb or kg) will also be collected.

Vital signs will be measured at screening and within 30 minutes before and 30 ±5 minutes after administration of IP, at each study visit, and at study completion/termination. 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.

12.9 Karnofsky Performance Test

The Karnofsky Performance Test is a status scale (0 to 100) utilized to measure the level of activity and medical care requirements in subjects. It is an investigator based assessment of patient status which evaluates the subjects' ability to carry on normal life activities, as well as the symptoms of their disease.[20] Subjects will be scored using this scale at screening.

12.10 Special Treatment Considerations

Patients will be screened for eligibility in the study as described in the inclusion/exclusion criteria (Section 9.1 and Section 9.2), and will be informed of the study specific restrictions and requirements of the study. Patients who are not willing to comply with the study requirements and restrictions of the study will not be eligible for enrollment.

All biological agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include, but are not limited to:

- skin rash
- pruritus (itching)
- urticaria (hives)
- angioedema (for example, swelling of the lips and/or tongue)
- anaphylactic reaction.

Proteins may also cause redness, itching, swelling, or pain locally at the infusion site.

Sometimes, these reactions can be life-threatening. Therefore, all patients should be closely monitored for signs or symptoms that could result from such reactions, educated on the signs or symptoms of these types of reactions, and instructed to contact the study site immediately if any of the symptoms are experienced following an injection. If a patient experiences an acute allergic/hypersensitivity reaction after an injection of investigational product, he or she should be managed appropriately and given instruction to receive relevant supportive care. Additionally, for an event judged by the investigator to be a potential systemic allergic/hypersensitivity reaction, a blood sample should be drawn to test for anti-drug antibodies.

Patients who experience a potentially severe allergic reaction will be discontinued from study drug, they will complete a Termination/Study Completion Visit, and will be monitored for stabilization, or resolution of the AE. Premedications to prevent allergic reactions will not be permitted as severe allergic reactions are an outcome measure for this study.

13. STATISTICS

All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the statistical analysis plan (SAP).

13.1 Sample Size and Power Calculations

The sample size of at least 10 surgeries in 10 evaluable male subjects (at least 5 major surgeries in 5 evaluable subjects), as defined in the protocol, was chosen to provide sufficient evidence of safety and effectiveness for this indication and is not based on statistical considerations.

Evaluable subjects are defined as subjects who met all study entry criteria and who had all the 3 hemostatic efficacy assessments as per Section 8.4.1.

13.2 Analysis Sets

Classification into the analysis sets will be conducted prior to the database lock.

13.2.1 Safety Analysis Set

The safety analysis set (SAS) will be comprised of all subjects who received any amount of BAX 802.

13.2.2 Efficacy Datasets

13.2.2.1 Full Analysis Set

The full analysis set (FAS) will be comprised of all surgeries with at least 1 available hemostatic assessment.

13.2.2.2 Per-Protocol Analysis Set

The per-protocol analysis set (PP) will be comprised of all surgeries with evaluable ratings for all 3 perioperative hemostatic efficacy assessments, whom subjects met all study entry criteria and had no major protocol violations that might impact hemostatic efficacy assessments.

13.3 Handling of Missing, Unused, and Spurious Data

All data will be evaluated as observed; no imputation method for missing values will be used. A subject who withdraws prior to the last planned observation in a trial period will be included in the analyses up to the time of withdrawal.

13.4 Methods of Analysis

For qualitative parameters, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of parameters will be presented. Quantitative parameters will be summarized by the population size (N for sample size and n for available data), mean, standard deviation, median, minimum, and maximum values.

13.4.1 Primary Outcome Measure

The primary efficacy measure will be the overall assessment of hemostatic efficacy assessed intraoperatively and at postoperative Day 1 (ie, the day following the day of surgery) by the surgeon and and perioperatively at Day 14 visit or discharge (whichever is earlier) by the investigator (hemophilia physician), and will be summarized by the GHEA score and rated “excellent”, “good”, “fair” and “none”.

A treatment success will be defined as a rating of excellent and/or good.

Owing the possibility of multiple surgeries per subject, the statistical entity on which the primary outcome measure will be reported is the surgery.

Point estimates and corresponding 2-sided exact confidence intervals (CIs) at the 90% confidence level will be calculated for the rate of hemostatic efficacy assessments with excellent/good outcome.

The primary efficacy analysis will be based on the FAS population. As a supportive analysis, the same analyses will also be carried out on the PP population.

Any blood loss which is considered as unrelated bleeding (defined as any bleeding occurring at a different anatomical site other than the surgery site during the postoperative period, see Section 11.2.5) will not be taken into account for while making assessment of hemostatic efficacy for the primary efficacy measure.

13.4.2 Secondary Outcome Measures

13.4.2.1 Secondary Hemostatic Efficacy Analysis

Where possible, secondary outcome measures will be reported at the surgery level rather than the subject level. Descriptive statistics will be used to summarize the actual blood loss and transfusion requirements, respectively.

The summary of average daily and total weight-adjusted doses (average through postoperative Day 14 or discharge [whichever is earlier]) of BAX 802 per subject as well as the occurrence of bleeding episodes will be provided using descriptive statistics.

For unrelated bleeding episodes in the postoperative period, descriptive statistics will be used to summarize the overall hemostatic efficacy rating at 24 ±2 hours after initiation of treatment and at resolution of bleed (if not resolved within 24 hours). Separate descriptive summaries of average daily and total weight-adjusted doses required to treat unrelated bleeding episodes will be provided.

The secondary efficacy analysis will be performed on the FAS only.

13.4.2.2 Safety Analysis

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by presenting the number and percentage of subjects having any AE, having an AE in each system organ class, and having each individual AE as reported by preferred term. In the summaries, AEs will be counted only once per patient. If a patient reports the same AE more than once, it will be counted with its worst severity and closest relationship to the study product.

The number of subjects who experienced SAEs and the number of SAEs will be tabulated. In addition, the number of subjects who experienced AEs related to IP and the number of IP-related AEs will be tabulated and subcategorized for thrombotic events, inhibitory and total binding antibodies to rpFVIII and hFVIII, and binding antibodies to BHK proteins.

A listing of all AEs will be presented by subject identifier, age, preferred term, and reported term of the AE, duration, severity, seriousness, action taken, outcome, causality assessment, onset date, stop date, and medication or non-drug therapy to treat the AE. An overview table for AEs will be provided, presenting the number of AEs, the number of subjects with AEs and the corresponding percent of subjects in total, and by seriousness and relationship to study treatment. An additional summary table will present the total number of (mild, moderate, severe) AEs by system organ class and preferred term with relationship to IP.

Summary statistics over time will be presented for the continuous laboratory parameters. Descriptive statistics of changes from baseline (Day 0 - prior to surgery) by study visits will also be presented.

A frequency table of results of categorical laboratory parameters will be produced. Furthermore, laboratory abnormalities will be analyzed by shift tables where each subject will be counted only once with the worst grade in the summary tables.

All laboratory data will be listed with abnormal values.

Vital signs assessments as well as the corresponding changes from baseline will be summarized descriptively at each scheduled assessment.

The safety analysis will be based on the SAS.

13.5 Planned Interim Analysis of the Study

No interim analyses are planned for this study.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

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

15.1.1 Investigator Report and Final Clinical Study Report

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

15.2 Training

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

15.3 Monitoring

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

15.4 Safety Monitoring

The safety of the subjects in this study shall be monitored by an internal safety monitoring committee (ISMC).

The ISMC is an independent group consisting of various Baxalta employees who have experience and substantial expertise in the review and evaluation of safety data generated from study participants within this disease area and in the monitoring of safety of subjects

during the study. The ISMC will have a minimum of three members not directly involved with the conduct of the study, one of whom will serve as chair and another as secretary documenting decisions and ensuring appropriate communication to the study team. Membership of the ISMC will be drawn from Drug Safety/Pharmacovigilance, Clinical Research, Clinical Development, Data Management, and Biostatistics, who are not actively involved in the conduct of this study. The ISMC will review safety data at predefined intervals and make recommendations to the study team and the Program Innovation Team on study conduct including dose escalation and modifications to study plan. Details of the composition and responsibilities of the ISMC are provided in the ISMC charter.

The Sponsor plans to perform a safety analysis when data are available for 5 surgeries from adult subjects (with at least 2 major surgeries) to assess the suitability of studying BAX 802 in the peri-operative management of pediatric male subjects with CHA with inhibitors to hFVIII.

15.5 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 audit plan.

15.6 Non-Compliance with the Protocol

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

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

15.7 Laboratory and Reader Standardization

Not applicable; a central laboratory/reader will be used for all clinical assessments. Local laboratories are requested to provide their laboratory specifications for each assay used.

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 patients participate in this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information 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(s) 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(s) approval.

16.3 Informed Consent

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

All patients and/or their legally authorized representative must sign an ICF 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 ICF will be reviewed by the sponsor and approved by the EC and regulatory authority(s), where applicable, (see Section 16.2). The ICF 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 ICF, 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 ICF will be updated, if necessary. This new information and/or revised informed consent form that has 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).

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, screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

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

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

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

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

17.3 Document and Data Retention

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

18. FINANCING AND INSURANCE

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

19. PUBLICATION POLICY

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

20. SUPPLEMENTS

20.1 Procedures per Study Period

Table 8: Flow Diagram of Required Procedures for Baxalta Clinical Study 241502

1. Screening

Written Informed Consent must be obtained prior to any study-related procedures

Screening activities should be performed within 45 days prior to the planned elective surgery.

The following screening procedures are required:

- Eligibility evaluation (review of inclusion/exclusion criteria)
- Hemophilia history, bleeding episode history, history of aPCC or rFVIIA usage for a year prior to screening
- Relevant medical and surgical history and all medications taken 3 months prior to screening
- Review of concomitant medications/non-drug therapies
- Complete physical examination (see Section 12.6)
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measure body weight and height; see Section 12.8)
- Karnofsky performance test assessment (see Section 12.9)
- Clinical laboratory assessments (see Table 10).

Table 8: Flow Diagram of Required Procedures for Baxalta Clinical Study 241502

2. Preoperative Procedures (Day 0)

Subjects will return to the study site prior to their scheduled surgery as instructed by site staff. Subjects will undergo the following procedures:

Prior to surgery

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

- Accurate prediction of volume of expected blood loss intraoperatively (from completion of the procedure until approximately 24 hours post-surgery) and for the overall perioperative time period (up to discharge/end of study [EOS])

Loading Dose and Post Dosing Laboratory Assessment

Within 60 to 120 minutes before initiating surgery, the subject will receive a loading dose of BAX 802 to raise the plasma level of FVIII to ≥ 80% for major and to ≥ 50% for minor surgical, dental and invasive procedures.

Subjects will undergo the following procedures:

- **Prior to BAX 802 loading dose:**
  - Record AEs, concomitant medication and non-drug therapy use
  - Physical examination, vital signs (pulse, respiratory rate, blood pressure and temperature) and weight
  - Laboratory Assessments including:
    - Hematology (without differential but including platelets)
    - Clinical chemistry
    - Within 30 minutes before loading dose, blood draw for:
      - FVIII activity
- **BAX 802 loading dose:**
  - Loading dose of BAX 802 to raise the plasma level of FVIII to ≥ 80% of normal for major and to ≥ 50% for minor surgical, dental and invasive procedures. It will be administered within 60 to 120 minutes prior to surgery (prior to incision/intubation).
- **After BAX 802 loading dose:**
  - Laboratory assessment of FVIII activity: 30 ±5 minutes after infusion of the loading dose
  - Vital signs (pulse, respiratory rate, blood pressure and temperature) will be recorded 30 minutes after infusion
  - Confirmation that FVIII is adequate just prior to intubation/incision. Administration of additional dose of BAX 802, if required. If another dose of BAX 802 is necessary, an additional post-infusion FVIII activity determination must be performed 30 ±5 minutes following the infusion.
  - All samples taken through 6 hours post-infusion will be collected from an extremity other than that used for the infusion of study product. Thereafter, either extremity may be used to obtain samples.

The surgery may begin only if FVIII is in target range (Table 5 and Section 8.7.3.3.2).

Throughout: Monitoring of AEs and concomitant medication and non-drug therapy use.

Table 8: Flow Diagram of Required Procedures for Baxalta Clinical Study 241502

3. Intraoperative Procedures (Day 0)

During the surgical procedure:

- Record AEs and concomitant medication and non-drug therapy use
- Record blood product usage, including salvaged blood, packed red blood cells (pRBC), platelets, and other blood products.
- Administer additional BAX 802 infusions according to the dosing regimen (Table 5)
- Record intraoperative blood loss and transfusion requirements

If the subject has excessive or unexplained bleeding, blood draws for FVIII activity. Treat by whatever means necessary until adequate hemostasis is achieved. If rescue medications become necessary, the subject will subsequently be withdrawn from this BAX 802 surgery study.

After the surgical procedure:

- Record the volume of blood loss during surgery and total blood product usage, including salvaged blood, packed red blood cells (pRBCs), platelets, and other blood products
- Assess intraoperative hemostatic efficacy (Part A, Table 2) (at the end of surgery)
- Take sample for FVIII activity immediately after surgery completion, with dose adjustments as necessary on the day of surgery (see Section 10.5)
- Take sample for FVIII activity within preferably 4 to 6 hours following surgery, with dose adjustments as necessary on the day of surgery (see Section 10.5)

If the subject has excessive or unexplained bleeding, blood draws for FVIII activity. Treat by whatever means necessary until adequate hemostasis is achieved. If rescue medications become necessary (see Section 10.5), the subject will subsequently be withdrawn from this BAX 802 surgery study.

Table 8: Flow Diagram of Required Procedures for Baxalta Clinical Study 241502

4. Postoperative Procedures (Days 1 to 13)

- For subjects undergoing major surgery: keep pre-infusion FVIII levels at least at 80% of normal for the first postoperative 72 hours and at least at 50% during postoperative Day 4 to Day 7. It is recommended that the FVIII levels do not fall below 30% from Day 8 until discharge.
- For subjects undergoing minor surgery: keep pre-infusion FVIII levels at least at 50% of normal for the first postoperative 72 hours. It is recommended that the FVIII levels do not fall below 30% from Day 4 until discharge.

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

- Record AEs and concomitant medication and non-drug therapy use
- Record blood loss on a daily basis and at drain removal, if applicable
- Record transfusion requirements
- Global Hemostatic Efficacy Assessment (GHEA):
  - Part B (Table 3): assessment of postoperative hemostatic efficacy of BAX 802 performed at Day 1 by the operating surgeon/investigator
  - Part C (Table 4): assessment of perioperative hemostatic efficacy of BAX 802 at Day 14 or discharge (whichever is earlier) performed by the investigator

  If a subject leaves the facility on the day of the surgery/invasive procedure, it is required to have a site visit the next day (Day 1) and at Day 14 to perform the assessments of postoperative (Part B) and perioperative (Part C) hemostatic efficacy, respectively.
- Perform physical examination and vital signs (pulse, respiratory rate, blood pressure and temperature) on Days 1, 2, 3, and 7 post surgery (if a subject remains admitted).
- Blood draws for FVIII activity determination and hematology should be performed coincident with an early morning dose to the greatest extent possible.
- FVIII activity assays at the local and the central laboratories as per Section 8.7.3.3.3. Additional BAX 802 doses will be administered as per Table 5. FVIII activity assays pre infusion (within 30 minutes) and post infusion (30 ±5 minutes) for each IP administration, and at other time points as deemed necessary by the surgeon or investigator throughout the study
  - 1-stage clotting and chromogenic for the central laboratory
  - 1-stage clotting for local laboratories
- Samples for laboratory testing will be taken daily during Day 1 to 7 post-surgery and then subsequently once weekly:
  - Hematology
  - Clinical chemistry

- If the subject has excessive or unexplained bleeding, blood draws for FVIII activity. Treat by whatever means necessary until adequate hemostasis is achieved. If rescue medications become necessary, the subject will subsequently be withdrawn from this BAX 802 surgery study.

Table 8: Flow Diagram of Required Procedures for Baxalta Clinical Study 241502

5. Day 14 ±3 days Visit/Discharge Visit/End of Study [EOS] Visit (Day 42 +7 days)

The Day 14 Visit will be performed if subject has not been discharged by then. The Discharge Visit will be performed when the subject is discharged, and the EOS Visit will be performed 42 to 49 days following the completion of the surgical procedure. In cases where the Discharge Visit would occur within 3 days of either the Day 14 or the EOS visit, the respective visits will be done as a single visit.

Procedures to be performed for each subject at Day 14 Visit/Discharge Visit/EOS Visit:

- Perform overall perioperative hemostatic efficacy assessment (Part C) on Day 14 or discharge (whichever is earlier) by the investigator (hemophilia physician)
- Assessment of blood loss
- Assessment of transfusion requirements
  - Review of concomitant medications/non-drug therapies
  - Complete physical examination
  - AE monitoring
  - Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measure body weight)
- Clinical laboratory assessments (Table 10)
- Immunogenicity assays:
  - Anti-pFVIII and hFVIII binding and inhibitory antibody titers (Note: these will be performed only if at least 72 hours must have elapsed since the previous BAX 802 administration)
  - Anti-BHK binding antibody titers

6. Optional Antibody Testing Visit

Whenever feasible, a visit will be performed between 7 to 14 days after the subject is discharged. Study procedures will be performed as per Table 9 and blood samples will be collected for antibody testings and other tests as per Table 10. This visit is optional.

Procedures to be performed for each subject at Optional Antibody Testing Visit:

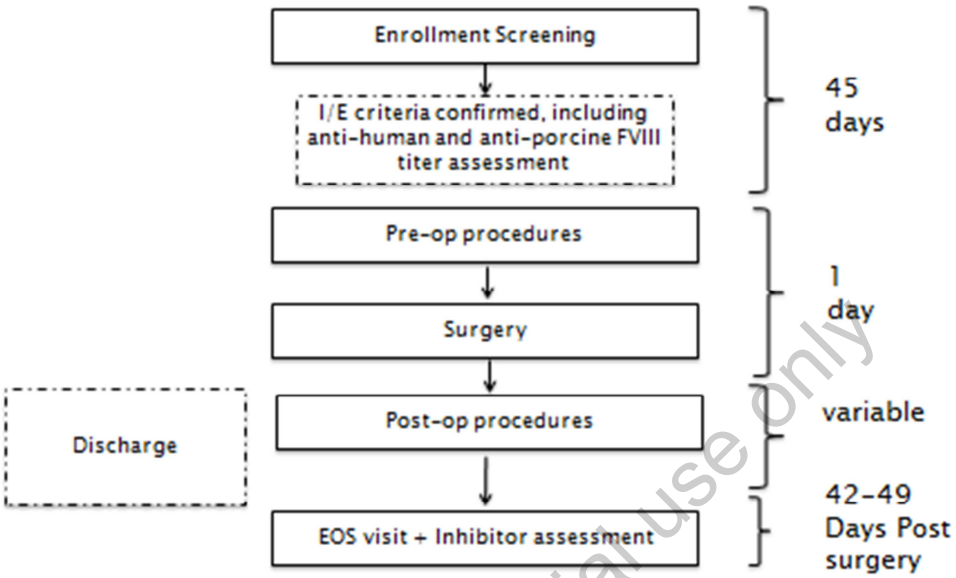
- Immunogenicity assays:
  - Anti-pFVIII and hFVIII binding and inhibitory antibody titers (Note: these will be performed only if at least 72 hours must have elapsed since the previous BAX 802 administration)
  - Anti-BHK binding antibody titers

Unrelated Bleeding Episodes During the Postoperative Period:

An unrelated bleeding episode is defined as any bleeding occurring at a different anatomical site than the surgery site during the postoperative period. Refer to Section 11.2.5, Table 9, and Table 10.

20.2 Study Flow Chart

Figure 1: Visit Schedule



20.3 Schedule of Study Procedures and Assessments

Table 9: Schedule of Study Procedures and Assessments

Period	**Screening**	**Preoperative procedures**	**Intraoperative procedures**	**Postoperative: Daily procedures; until subject is discharged**	**Day 14 ±3 or Discharge (whichever is earlier) procedures[a]**	**Optional Antibody Testing Visit[b]**	**End of Study Visit[c]/ Discharge procedures[a]**
Procedure/Assessment	**Up to 45 days prior to Day 0**	**Day 0 ~1 to 2 hours prior to surgery**	**Day 0 During surgery**	**Day 1 to Day 13**	**Day 14 ±3 Discharge day**	**Between 7 to 14 days after the Discharge day**	**Day 42 +7 Discharge day**
Eligibility criteria, including medical history[d]	X						
Medications and non-drug therapies	X	X	X	X	X	X	X
Physical examination	X	X		X[e] (as required)	X	X	X
Adverse events		X	X	X	X	X	X
Laboratory assessments[f]	X	X	X	X	X	X	X
Vital signs[g]	X	X[h]	X[h]	X[e,h]	X	X	X
Karnofsky Performance Test	X						
Approved FVIII maintenance plan		X					
IP treatment		X (loading dose; Table 5)	X (as required; Table 5)	X (as required; Table 5)	X (as required; Table 5)		
Hemostatic Efficacy Assessments			A at the end of surgery as per Table 2	B at 24 hours (Day 1) as per Table 3[i]	C at Day 14 or discharge (whichever is earlier), as per Table 4[i]		
Transfusion requirements			X	X	X		X

Table 9: Schedule of Study Procedures and Assessments

Period	**Screening**	**Preoperative procedures**	**Intraoperative procedures**	**Postoperative: Daily procedures; until subject is discharged**	**Day 14 ±3 or Discharge (whichever is earlier) procedures[a]**	**Optional Antibody Testing Visit[b]**	**End of Study Visit[c]/ Discharge procedures[a]**
Procedure/Assessment	**Up to 45 days prior to Day 0**	**Day 0 ~1 to 2 hours prior to surgery**	**Day 0 During surgery**	**Day 1 to Day 13**	**Day 14 ±3 Discharge day**	**Between 7 to 14 days after the Discharge day**	**Day 42 +7 Discharge day**
Procedures for Unrelated Bleeding Episodes During the Postoperative Period (see Section 11.2.5)							
Medications and non-drug therapies		X					
Laboratory assessments		Refer to Table 10					
IP treatment		Refer to Table 6					
Vital signs[g]		X[h]					
Hemostatic Efficacy Assessments		At 24 ±2 hours after the initiation of treatment and at the resolution of bleed (if not resolved within 24 hours) using a 4-point efficacy rating scale (Table 7)					
Transfusion requirements		X					

[a] In cases where the Discharge Visit would occur within 3 days of either the Day 14 or the End of Study Visit, the respective visits will be done as a single visit.
[b] This visit is optional.
[c] This visit also applies to subjects who withdraw or discontinue prematurely.
[d] Occurs prior to any study-specific procedures.
[e] Perform physical examination and vital signs (pulse, respiratory rate, blood pressure and temperature) on Days 1, 2, 3, and 7 post surgery (if a subject remains admitted).
[f] For laboratory assessments, see Table 10.
[g] Vital signs will include body temperature, pulse rate, blood pressure, respiratory rate, and weight. Blood pressure will be measured when subjects are in the supine position. Height, measured once at Screening, will also be collected.
[h] Within 30 minutes pre, 30 ±5 minutes post-dose.
[i] If the subject is discharged from surgical facility on the day of the procedure, he should attend the site on Day 1 to perform the postoperative hemostatic efficacy assessment (Day 1 assessment) and the overall peri-operative assessment. In this case, physical examination, vital signs, laboratory assessments, adverse events, and concomitant medications must also be assessed.

20.4 Clinical Laboratory Assessments

Table 10: Clinical Laboratory Assessments

			Preoperative Period		**Postoperative Period**			
Period		**Screening**	**Preoperative procedures**	**Intraoperative procedures**	**Postoperative: daily procedures; till subject is discharged**	**Day 14 ±3 or Discharge (whichever is earlier) procedures[a]**	**Optional Antibody Testing Visit[b]**	**End of Study Visit[c]/ Discharge procedures[a]**
Assessment	**Sample**	**Up to 45 days prior to Day 0**	**Day 0 ~1 to 2 hours Prior to Surgery**	**Day 0 During surgery**	**Day 1 to Day 13**	**Day 14 ±3 Discharge day**	**Between 7 to 14 days after the Discharge day**	**Day 42 +7 Discharge day**
FVIII activity (clotting *and* chromogenic assay at central lab; clotting assay at local lab)	Citrated plasma	C	L and C within 30 minutes before loading dose, then 30 ±5 minutes after loading dose[d]	Optional sampling, as deemed necessary: L and C Also, if subject has excessive or unexplained bleeding	L and C[e]	L and C		L and C
PT and aPTT	Citrated plasma	C and L						
Chemistry[f]	Serum	C	L and C	(L)	L Daily Days 1 to 7	C (L)	C (L)	C (L)
Hematology	Whole blood	C[g]	L[h]	(L)	L Daily Days 1 to 7	C (L)	C (L)	C (L)
Urinalysis	Urine	C				C	C	C
Viral serology[i]	Serum[j]	C						

Table 10: Clinical Laboratory Assessments

			Preoperative Period		Postoperative Period			
Period		**Screening**	**Preoperative procedures**	**Intraoperative procedures**	**Postoperative: daily procedures; till subject is discharged**	**Day 14 ±3 or Discharge (whichever is earlier) procedures[a]**	**Optional Antibody Testing Visit[b]**	**End of Study Visit[c]/ Discharge procedures[a]**
Assessment	**Sample**	**Up to 45 days prior to Day 0**	**Day 0 ~1 to 2 hours Prior to Surgery**	**Day 0 During surgery**	**Day 1 to Day 13**	**Day 14 ±3 Discharge day**	**Between 7 to 14 days after the Discharge day**	**Day 42 +7 Discharge day**
Anti-pFVIII and hFVIII binding and inhibitory antibody titers	Citrated plasma	C[g]				C[k]	C	C[k]
Anti-BHK binding Antibody titers	Citrated plasma	C				C	C	C
Laboratory Assessments for Unrelated Bleeding Episodes During the Postoperative Period (see Section 11.2.5)								
FVIII activity (clotting *and* chromogenic assay at central lab; clotting assay at local lab)	Citrated plasma	Refer to Section 11.2.5 Optional sampling, as deemed necessary: L and C						

Key: C = central laboratory; L = local laboratory; (L) = local testing optional, to aid in clinical management of patients.

[a] In cases where the Discharge Visit would occur within 3 days of either the Day 14 or the End of Study visit, the respective visits will be done as a single visit.

[b] This visit is optional.

[c] This visit also applies to subjects who withdraw or discontinue prematurely.

[d] It is recommended that the surgery starts after FVIII levels have achieved target levels. If FVIII activity post loading dose is close to the target level, a supplement dose of BAX 802 should be administered without further delaying the surgery. If FVIII activity post loading dose is not close to the target level, a supplement dose of BAX 802 should be administered and surgery delayed until FVIII levels have achieved target levels or are in close range.

[e] FVIII activity should be monitored postoperatively as per instructions in Section 8.7.3.3.3.

Continued on Next Page

Continued

[f] Sodium, potassium, chloride, bicarbonate, protein, albumin, ALT, AST, total bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, and glucose.

[g] Hematology and antibody testing should be performed during the screening at least 2 weeks before the planned surgery day as hematocrit and anti-pFVIII inhibitor titer values are required for loading dose calculation.

[h] Hematology, without differential but including platelets.

[i] HIV-1 and HIV-2 antibody, HAV (IgM and total antibodies), HBsAg, HBsAb, HBcAb, HCV Ab, and parvovirus B19 (IgM and IgG antibodies). CD4 for HIV positive patients and HCV-RNA or HIV-RNA for confirmatory testing of HIV or HCV positive results, respectively.

[j] Citrated plasma for HCV-RNA or HIV-RNA confirmatory testing.

[k] To be performed only if at least 72 hours must have elapsed since the previous BAX 802 administration.

20.5 Global Efficacy Assessments Scores

Table 11: Combinations of Individual Efficacy Assessments (A, B, C) and GHEA Score

Individual Assessment Scores (A,B,C)	GHEA
3 3 3	Excellent
3 3 2	Excellent
3 2 2	Excellent
3 3 1	Good
3 2 1	Good
3 1 1	Good
2 2 2	Good
2 2 1	Good
2 1 1	Fair
1 1 1	Fair
3 3 0	None
3 2 0	None
3 1 0	None
3 0 0	None
2 2 0	None
2 1 0	None
2 0 0	None
1 1 0	None
1 0 0	None
0 0 0	None

20.6 Definitions

20.6.1 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.

20.6.2 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.[5,21]

21. REFERENCES

1. Coppola A, Di Capua M, Di Minno MND et al. Treatment of hemophilia: A review of current advances and ongoing issues. J.Blood Med. 2010;1:183-195.
   Link to Publisher´s Site:
   http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3262316/pdf/jbm-1-183.pdf

2. Janbain M, Leissinger CA, Kruse-Jarres R. Acquired hemophilia A: emerging treatment options. J.Blood Med. 2015;6:143-150.
   Link to Publisher´s Site:
   http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4431493/pdf/jbm-6-143.pdf

3. Mansouritorghabeh H. Clinical and laboratory approaches to hemophilia A. Iran.J.Med.Sci. 2015;40:194-205.
   Link to Publisher´s Site:
   http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4430880/pdf/ijms-40-194.pdf

4. Berntorp E, Shapiro A, Astermark J et al. Inhibitor treatment in haemophilias A and B: summary statement for the 2006 international consensus conference. Haemophilia. 2006;12 Suppl 6:1-7.

5. World Federation of Hemophilia Treatment Guidelines Working Group. Guidelines for the management of hemophilia 2nd Edition. 76. 2005. World Federation of Hemophilia (WFH).
   Link to Publisher´s Site: http://www1.wfh.org/publication/files/pdf-1472.pdf

6. Santagostino E, Escobar M, Ozelo M et al. Recombinant activated factor VII in the treatment of bleeds and for the prevention of surgery-related bleeding in congenital haemophilia with inhibitors. Blood Rev. 2015;29 Suppl 1:S9-S18.

7. Valentino LA, Cooper DL, Goldstein B. Surgical experience with rFVIIa (NovoSeven) in congenital haemophilia A and B patients with inhibitors to factors VIII or IX. Haemophilia. 2011;17:11-579.

8. Kempton CL, White GC, II. How we treat a hemophilia A patient with a factor VIII inhibitor. Blood. 2009;113:11-17.

9. Kasper CK. Effect of prothrombin complex concentrates on factor VIII inhibitor levels. Blood. 1979;54:1358-1368.

10. Young G, Sørensen B, Dargaud Y et al. Thrombin generation and whole blood viscoelastic assays in the management of hemophilia: current state-of-art and future perspectives. Blood. 2013;121:1944-1950.

11. Kempton CL, Abshire TC, Deveras RA et al. Pharmacokinetics and safety of OBI-1, a recombinant B domain-deleted porcine factor VIII, in subjects with haemophilia A. Haemophilia. 2012;18:798-804.

12. Mahlangu J, Andreeva T, Macfarlane D et al. A phase II open-label study evaluating the hemostatic activity, pharmacokinetics and safety of recombinant porcine factor VIII (OBI-1) in hemophlia A patients with inhibitors directed against human FVIII [abstract]. Haemophilia. 2008;14 Suppl 2:15-16.

13. Kruse-Jarres R, St Louis J, Greist A et al. Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A. Haemophilia. 2015;21:162-170.

14. Baxter Healthcare Corporation. Obizur core data sheet. 7-22-2015.

15. Brettler DB, Forsberg AD, Levine PH et al. The use of porcine factor VIII concentrate (Hyate:C) in the treatment of patients with inhibitor antibodies to factor VIII. A multicenter US experience. Arch.Intern.Med. 1989;149:1381-1385.

16. Hay CRM, Lozier JN, Lee CA et al. Safety profile of porcine factor VIII and its use as hospital and home-therapy for patients with haemophilia-A and inhibitors: the results of an international survey. Thromb.Haemost. 1996;75:25-29.

17. Baxter Healthcare Corporation. Package Insert: OBIZUR [antihemophilic factor (recombinant), porcine sequence] lyophilized powder for solution for intravenous injection. 10. 2014. OBIZUR.

18. Lee CA. The evidence behind inhibitor treatment with porcine factor VIII. Pathophysiol.Haemost.Thromb. 2002;32 Suppl 1:5-8.

19. Kasper, C. Diagnosis and Management of Inhibitors to Factors VIII and IX - An Introductory Discussion for Physicians. Treatment of Hemophilia (34), 22. 2004. World Federation of Hemophilia (WFH).
Link to Publisher´s Site: http://www1.wfh.org/publications/files/pdf-1178.pdf

20. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, ed. Evaluation of Chemotherapeutic Agents. New York: Columbia University Press; 1949:191-205.

21. Blanchette VS, Key NS, Ljung LR et al. Definitions in hemophilia: Communication from the SSC of the ISTH. J.Thromb.Haemost. 2014;12:1935-1939.

22. SUMMARY OF CHANGES

Protocol 241502: Amendment 1, 2016 FEB 03

Replaces: Original: 2015 SEP 30

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

2. Synopsis, Secondary Objectives, Secondary Outcome Measure, and Planned Statistical Analysis; Section 7.3, Secondary Objectives; Section 8.4.2.1, Efficacy; Section 11.2.5, Hemostatic Efficacy Rating for Treatment of Unrelated Bleeding Episodes; Section 13.4.1, Primary Outcome Measure; Section 13.4.2.1, Secondary Hemostatic Efficacy Analysis; Table 8, Flow Diagram of Required Procedures for Baxalta Clinical Study 241502
   Description of Change: Change from "intercurrent, unrelated bleeding episodes" to "unrelated bleeding episodes.
   Purpose for Change: Editorial.

3. Synopsis, Primary Outcome Measure, Secondary Outcome Measures, and Planned Statistical Analysis; Section 8.4.1, Primary Outcome Measure; Table 4, Postoperative Efficacy Assessment Scale (Day 14); Section 8.4.2.1, Efficacy; Section 11.2.2, Blood Transfusions; Section 12.7.3, Immunogenicity; Table 8, Flow Diagram of Required Procedures for Baxalta Clinical Study 241502; Table 9, Schedule of Study Procedures and Assessments
   Description of Change: Amended "Day 14" to "Day 14 or discharge (whichever is earlier)". In addition, "postoperative" was amended to read "overall perioperative". Table 4 was amended in line with the changes detailed.
   Purpose for Change: To ensure that the efficacy data is captured at the appropriate time.

4. Synopsis, Secondary Objectives; Section 7.3, Secondary Objectives; Section 8.4.2.1, Efficacy
   Description of Change: Clarity added regarding the "overall perioperative" time point. Changed as follows: "Intra- and postoperative and overall perioperative blood loss compared to the estimated volume of expected average blood loss and expected maximum blood loss in a comparable healthy individual as predicted preoperatively by the investigator/surgeon…"

Purpose for Change: To ensure that the efficacy data is captured at the appropriate time.

5. Synopsis, Secondary Outcome Measures; Section 8.4.2.1, Efficacy
Description of Change: "Intra- and postoperative blood loss" changed to "Blood loss…"
Purpose for Change: To ensure that the efficacy data is captured at the appropriate time.

6. Synopsis, Active Product; Section 8.7.3.3.3, Postoperative Dosing; Section 11.3, Factor VIII Activity
Description of Change: Change from "intravenous bolus" to "intravenous infusion" and from "re-bolus" to "re-dosing".
Purpose for Change: Changed as given as intravenous infusion and not bolus.

7. Synopsis, Subject Selection
Description of Change: "10 evaluable adult male subjects (≥ 18 to ≤ 65 years old) with CHA with inhibitors to FVIII undergoing surgical and other invasive procedures for efficacy and safety evaluation" deleted.
Purpose for Change: Editorial.

8. Synopsis, Inclusion Criteria; Section 9.1, Inclusion Criteria
Description of Change: Change in inclusion criterion 5 to "Subject is not currently receiving or has recently received (< 30 days) ITI therapy".
Purpose for Change: To clarify the washout period for ITI therapy.

9. Synopsis, Exclusion Criteria; Section 9.2, Exclusion Criteria
Description of Change: Change in exclusion criterion 7 to "Subject has another active coagulation disorder, other than hemophilia A, as per the medical history". Change in exclusion criterion 10 to remove "OR subject has been exposed to rpFVIII (OBIZUR) before".
Purpose for Change: To clarify that another active coagulation disorder can be documented as per the medical history and to remove exclusion regarding OBIZUR.

10. Synopsis, Study Design and Sample Size Calculation; Section 6.3, Population To Be Studied; Section 8.1, Brief Summary; Section 8.2, Overall Study Design; Section 13.1, Sample Size and Power Calculation

Description of Change: Clarity added regarding the sample size of 10 being based on at least 10 surgeries in 10 evaluable male subjects-and at least 5 surgeries in 5 evaluable subjects.
Purpose for Change: To ensure sufficient evidence is gathered regarding safety and effectiveness for BAX 802 in this indication.

11. Synopsis, Planned Statistical Analysis; Section 13.2.2.1, Full Analysis Set; Section 13.2.2.2, Per-Protocol Analysis Set
Description of Change: Definitions of FAS and PP analysis set amended. Second paragraph deleted.
Purpose for Change: To clarify analysis set definitions.

12. Synopsis, Planned Statistical Analysis; Section 13.4.1, Primary Outcome Measure; Section 13.4.2.1, Secondary Hemostatic Efficacy Analysis
Description of Change: The primary outcome measure was clarified in line with changes to Section 8.4.1, clarity added regarding unrelated bleeding, and details added regarding the primary outcome measure in the case of multiple surgeries and reporting of secondary outcome measures at the surgery rather than subject level.
Purpose for Change: To ensure that the efficacy data is captured at the appropriate time.

13. Section 5, List of Abbreviations
Description of Change: Added new abbreviations (aPTT, AST, RSI). Added "Continued" at the top of each page of the List of Abbreviations per Baxalta style guide.
Purpose for Change: Administrative.

14. Section 5, List of Abbreviations; Section 6.6, Compliance Statement
Description of Change: Definition of ICH amended to "International Council for Harmonisation".
Purpose for Change: Administrative.

15. Section 6.4.2, Findings from Clinical Studies
Description of Change: Text updated with the following "As of 2015 December 31, there have been 4 post-marketing spontaneous serious adverse event reports. The reports were considered possibly associated and consistent with the known safety profile of OBIZUR®".
Purpose for Change: To align with current information.

16. Section 6.6, Compliance Statement; Section 10.1, Informed Consent; Section 10.2, Subject Identification Code; Section 10.3, Screening and Study Visits; Section 12.1.1.3, Unexpected Adverse Events; Section 12.1.2.3, Safety Reporting; Section 12.2, Urgent Safety Measures; Section 12.5, Medical, Medication, and Non-Drug Therapy History; Section 12.7.5, Backup Samples and Biobanking; Section 13.2, Analysis Sets; Section 15.5, Auditing; Section 16.2, Ethics Committee and Regulatory Authorities; Section 16.3, Informed Consent; Section 17.2, Study Documentation and Case Report Forms; Table 9, Schedule of Study Procedures and Assessments
Description of Change: Minor changes have been made to align the protocol with standard text presented in the current Baxalta protocol template.
Purpose for Change: Administrative.

17. Section 8.2, Overall Study Design
Description of Change: Deletion of the text as follows: "Subjects may undergo more than 1 surgery or 2 parallel surgeries, such as bilateral knee replacement~~, however, in these cases prior approval by the sponsor is required~~" and text added to describe the process to be followed for subjects undergoing multiple surgeries (other than parallel surgeries).
Purpose for Change: To remove requirement for sponsor approval and to provide clarity regarding visits for subjects undergoing multiple surgeries.

18. Section 8.2.2, Dose Selection Rationale
Description of Change: Deletion of the following text: "This regimen for loading dose of BAX 802 proposed for Study BAX 802 Surgery takes into account the titer of anti-pFVIII inhibitors".
Purpose for Change: Editorial.

19. Section 8.4.1, Primary Outcome Measure
Description of Change: Addition of the following text: "The assessment of primary outcome measure (GHEA score) should only account for the blood loss related to the surgery and exclude any blood loss which is considered as unrelated bleeding (defined as any bleeding occurring at a different anatomical site than the surgery site during the postoperative period, see Section 11.2.5)".
Purpose for Change: Revised to make distinction between blood loss due to surgery and unrelated blood loss.

20. Section 8.7.3.1, FVIII Maintenance Plan
Description of Change: Addition of the following text: "It is recommended that the turnaround time for FVIII activity results from the local laboratories are ≤ 2 hours so that dosing decisions could be made and subjects are dosed adequately".
Purpose for Change: Revised as good turnaround time will ensure that subjects are dosed as needed, and also allows better monitoring.

21. Section 8.7.3.3.1, General; Table 5, Dosing for Perioperative Management
Description of Change: Deletion of the following text: "The dose and frequency of BAX 802 administered will be individualized based on the subject's PK parameters for major surgeries and the most recent IR value for minor surgeries and the required FVIII target levels". In addition, the units in the "Required dose" calculation were amended from "IU" to "U", while clarity was added to Table 5 regarding subjects not yet being discharged and a 1- to 2-hour window for administration of the loading dose prior to surgery was added.
Purpose for Change: Pharmacokinetic parameters are not being measured in this study.

22. Section 8.7.3.3.2, Preoperative and Loading Dose
Description of Change: Clarity added regarding a 1 to 2 hour window for administration of the loading dose prior to surgery. In case of surgery, FVIII target levels amended to ≥ 80% for major surgeries/procedures and ≥ 50% for minor surgeries/procedures. In addition, recommendations were added/clarified.
Purpose for Change: To ensure that the efficacy data is captured at the appropriate time.

23. Section 8.7.3.3.3, Postoperative Dosing
Description of Change: Section replaced with new text.
Purpose for Change: To ensure that the efficacy data is captured at the appropriate time.

24. Section 8.7.3.3.4, Dosing for Unrelated Bleeding Episodes During the Postoperative Period
Description of Change: Text amended as follows: "Infusions given to ~~maintain hemostatis~~ treat and control the unrelated bleeding episode should be documented in the eCRF".
Purpose for Change: Editorial.

25. Table 6, BAX 802 Treatment Guidelines for Unrelated Bleeding Episodes
Description of Change: Units amended from "IU" to "U", "Loading Dose" and "Subsequent Dose" columns replaced with 1 "BAX 802 Dose" column, footnotes updated, other minor edits.
Purpose for Change: Administrative.

26. Section 8.8, Source Data
Description of Change: Statement added regarding data not being entered directly onto the CRF.
Purpose for Change: Administrative.

27. Section 10.4.2, Unscheduled Visits for Unrelated Bleeding Episodes
Description of Change: Section 10.4.2 replaced with new section on "Optional Antibody Testing Visit". Details of the optional antibody testing visit also added to Table 8.
Purpose for Change: Unscheduled visits no longer applies, while a visit for testing of antibody titers has been added. The antibody testing visit is optional so that there will be no additional burden on subjects; it will be done when feasible.

28. Section 11.2.5, Hemostatic Efficacy Rating for Treatment of Inter-current, Unrelated Bleeding Episodes; Table 8, Flow Diagram of Required Procedures for Baxalta Clinical Study 241502
Description of Change: Clarity added regarding the treatment of unrelated bleeding episodes occurring during the subject's stay in hospital.
Purpose for Change: To provide clearer information.

29. Table 7, Efficacy Rating Scale for Treatment of Bleeding Episodes
Description of Change: Clarified that table refers to "unrelated" bleeding episodes.
Purpose for Change: Administrative.

30. Section 11.3, Factor VIII Activity; Table 8, Flow Diagram of Required Procedures for Baxalta Clinical Study 241502; Table 10, Clinical Laboratory Assessments
Description of Change: Timing of collection of preoperative blood samples for assessment of FVIII activity amended from 60 to 30 minutes prior to the administration of the initial loading dose, and timing for collection of postoperative blood samples for assessment of FVIII activity amended from 15 to 30 ±5 minutes post-infusion.
Purpose for Change: To ensure that the efficacy data is captured at the appropriate time.

31. Section 11.3.1, Blood Sampling and Processing for FVIII Analysis; Table 8, Flow Diagram of Required Procedures for Baxalta Clinical Study 241502; Table 10, Clinical Laboratory Assessments
Description of Change: Clarified that local laboratories will only use a 1-stage clotting assay for determination of FVIII activity.
Purpose for Change: Administrative.

32. Section 12.7, Clinical Laboratory Parameters; Section 12.7.1, Hematology, Clinical Chemistry, and Urinalysis; Table 10, Clinical Laboratory Assessments
Description of Change: Aspartate aminotransferase added to clinical chemistry panel, and "bilirubin" amended to "total bilirubin".
Purpose for Change: AST was inadvertently omitted from the original protocol and clarification was added regarding total bilirubin to avoid confusion with direct or indirect bilirubin.

33. Section 12.7.2, Viral Serology
Description of Change: HAV antibody replaced with HAV IgM and total antibodies and HBsAb and HBcAb added. In addition, clarity added that HIV titer was also to be confirmed by PCR for all subjects reported as HIV positive and that any positive HBsAg test was to be repeated using a new blood sample.
Purpose for Change: To clarify the specific serology testing to be performed.

34. Section 12.7.3, Immunogenicity
Description of Change: Reference to BAX 802 inhibitor assay, local laboratories, and reference for details of laboratory pre-qualification removed.
Purpose for Change: Editorial.

35. Section 12.7.5, Backup Samples and Biobanking
Description of Change: Examples of "other test results" added; FVIII activity and antibody testing.
Purpose for Change: Editorial.

36. Section 12.8, Vital Signs; Table 8, Flow Diagram of Required Procedures for Baxalta Clinical Study 241502; Table 9, Schedule of Study Procedures and Assessments
Description of Change: Timing of measurement of vital signs amended from 15 to 30 ±5 minutes after administration of IP.
Purpose for Change: To ensure that the safety data is captured at the appropriate time.

37. Section 13, Statistics
Description of Change: Text deleted as follows: "~~Data handling will be the responsibility of the contract research organization (CRO). The data will be inspected for inconsistencies by performing validation checks.~~
All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the statistical analysis plan (SAP) ~~prepared by the CRO and approved by the sponsor before database lock~~".
Purpose for Change: Not standard Baxalta template text.

38. Section 13.1, Sample Size and Power Calculations
Description of Change: Text added as follows: "Evaluable subjects are defined as subjects who met all study entry criteria and who had all the 3 hemostatic efficacy assessments as per Section 8.4.1".
Purpose for Change: Administrative.

39. Section 13.5, Planned Interim Analysis of the Study
Description of Change: Section amended to reflect that no interim analyses are planned for this study.
Purpose for Change: Administrative.

40. Section 15.4, Safety Monitoring; Section 16.4, Data Monitoring Committee
Description of Change: Updated to include details of ISMC, new section added, and details from Section 16.4 integrated with new section to align with current Baxalta protocol template; Section 16.4 deleted.
Purpose for Change: Administrative.

41. Table 8, Flow Diagram of Required Procedures for Baxalta Clinical Study 241502; Table 10, Clinical Laboratory Assessments
Description of Change: Timing of sample collection for FVIII activity on Day 0 updated. In addition, under "Procedures to be performed for each subject at Day 14 Visit/Discharge Visit/EOS Visit", text has been changed as follows: "Perform ~~Postoperative Hemostatic Efficacy Assessment~~ overall perioperative efficacy assessment (Part C) on Day 14 or discharge (whichever is earlier) by the investigator (hemophilia physician)." Timing for administration of the loading dose prior to surgery amended to a 1 to 2 hour window.
Purpose for Change: To ensure that the efficacy data is captured at the appropriate time.

42. Section 20.2, Study Flow Chart
Description of Change: Figure 1 (Visit Schedule) replaced with new figure.
Purpose for Change: For consistency with changes to earlier protocol sections.

43. Table 9, Schedule of Study Procedures and Assessments
Description of Change: Additional information added, including procedures for unrelated bleeding episodes during the postoperative period, and optional antibody testing visit added.
Purpose for Change: To add clarity and include relevant information regarding assessments needed for unrelated bleeding.

44. Table 10, Clinical Laboratory Assessments
Description of Change: aPTT added to assessments, footnotes updated, additional information added regarding laboratory assessments for unrelated bleeding episodes during the postoperative period, back-up samples for central laboratory testing of FVIII activity removed, and optional antibody testing visit added.
Purpose for Change: To ensure that the clinical laboratory assessments are captured at the appropriate time.

45. Table 11, Schedule of Study Procedures and Assessments for Unrelated Bleeding Episodes
Description of Change: Table deleted.
Purpose for Change: Deleted as now addressed in Tables 9 and 10.

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: BAX 802

STUDY TITLE: A Phase 3, Multicenter, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX 802) in the Treatment of Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures

PROTOCOL IDENTIFIER: 241502

CLINICAL TRIAL PHASE 3

AMENDMENT 1: 2016 FEB 03

Replaces: ORIGINAL: 2015 SEP 30

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: to be determined
IND NUMBER: to be determined

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: BAX 802

STUDY TITLE: A Phase 3, Multicenter, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX 802) in the Treatment of Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures

PROTOCOL IDENTIFIER: 241502

CLINICAL TRIAL PHASE 3

AMENDMENT 1: 2016 FEB 03

Replaces: ORIGINAL: 2015 SEP 30

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: to be determined
IND NUMBER: to be determined

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

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD
[redacted], Clinical Development

CLINICAL STUDY PROTOCOL

PRODUCT: BAX 802

STUDY TITLE:
A Phase 3, Multicenter, Single-arm, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX 802) in Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures

STUDY SHORT TITLE: BAX 802 in Congenital Hemophilia A with Inhibitors

PROTOCOL IDENTIFIER: 241502

CLINICAL TRIAL PHASE 3

AMENDMENT 4: 2017 JUN 28

Replaces:

AMENDMENT 1: 2016 FEB 03

ALL VERSIONS:
Amendment 4: 2017 JUN 28
Amendment 3 (Russia): 2017 FEB 07
Amendment 2 (Italy): 2016 AUG 22
Amendment 1: 2016 FEB 03
Original: 2015 SEP 30

OTHER ID(s)
NCT Number: NCT02895945
EudraCT Number: 2015-005521-39
IND NUMBER: BB-IND 014798

Study Sponsor(s):

Baxalta US Inc.
One Baxter Way
Westlake Village, CA 91362,
UNITED STATES

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna,
AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted], Clinical Programs and Therapeutic Area Head
Baxalta Innovations GmbH

1.2 Study Organization

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

2. SERIOUS ADVERSE EVENT REPORTING

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

ALL SAEs, INCLUDING SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARs), ARE TO BE REPORTED ON THE ADVERSE EVENT CASE REPORT FORM (CRF) WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT. IF THE CRF 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 REQIREMENT.

Drug Safety contact information: see SAER form

Refer to SAE Protocol Sections and the study team roster for further information.

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

- AEs, Section 12.1
- SAE, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- Assessment of AEs, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	BAX 802
Name(s) of Active Ingredient(s)	Recombinant Porcine Factor VIII (rpFVIII)
CLINICAL CONDITION(S)/INDICATION(S) Congenital hemophilia A (CHA) patients with inhibitors to Factor VIII (FVIII) undergoing surgical and other invasive procedures	
PROTOCOL ID	241502
PROTOCOL TITLE	A Phase 3, Multicenter, Single-arm, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX 802) in Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures
Short Title	BAX 802 in CHA with Inhibitors
STUDY PHASE	Phase 3
PLANNED STUDY PERIOD	
Initiation	2016, FEB
Primary Completion	2019, MAR
Study Completion	2019 MAR
Duration	Approximately 21 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose To evaluate the efficacy and safety of BAX 802 in males with CHA with inhibitors who are undergoing major or minor elective surgical, dental, or other invasive procedures.	
Primary Objective To evaluate the perioperative hemostatic efficacy of BAX 802 in male subjects with CHA with inhibitors to human factor VIII (hFVIII) undergoing major or minor elective surgical, dental, or other invasive procedures as determined by the Global Hemostatic Efficacy Assessment (GHEA) score.	
Secondary Objectives 1. To determine the safety of BAX 802 used in the perioperative setting by assessing: • The development of and change in titer of anti-porcine FVIII (pFVIII) and anti-hFVIII antibodies (binding and neutralizing), and development of binding antibodies to baby hamster kidney (BHK) proteins • The occurrence of thrombo-embolic events and/or allergic reactions to BAX 802 • The occurrence of adverse events (AEs) related to BAX 802	

- The occurrence of clinically significant changes in vital signs and routine laboratory parameters related to BAX 802

2. To determine the intraoperative, postoperative, and overall perioperative blood loss, compared to the estimated volume of expected average and maximum blood loss in a comparable healthy individual as predicted preoperatively by the Investigator/surgeon
3. To determine the proportion of major surgeries with good or excellent hemostatic score
4. To determine the daily and total weight-adjusted administration of BAX 802 per subject

Exploratory objectives

[redacted]

STUDY DESIGN

Study Type/ Classification/ Discipline	Efficacy and Safety
Control Type	No control arm
Study Indication Type	Treatment
Intervention model	Single-group
Blinding/Masking	Open-label
Study Design	This study is a Phase 3, prospective, single-arm, open-label, uncontrolled, multicenter study to evaluate the efficacy and safety of BAX 802 in at least 12 procedures in 12 evaluable male subjects with CHA with inhibitors to hFVIII who are undergoing major or minor elective surgical, dental or other invasive procedures. The study will be conducted globally and will be divided into 5 periods: Screening, Preoperative, Intraoperative, Postoperative, and End of study.
Subject Selection	At least 5 of the procedures must be major surgeries in 5 evaluable subjects, of which no more than 20% can be dental or other non-operative invasive procedures. Elective surgical procedures will prospectively be defined as major or minor by the Investigator/surgeon, based on the protocol guidance and definitions and in consideration of each subject's characteristics. Emergency surgeries are not in the scope of this study.

	Subjects may undergo more than 1 surgery or 2 parallel surgeries, such as bilateral knee replacement, however in these cases prior approval by the sponsor is required. In order to evaluate the activity of the product with respect to high-titer or high-responding inhibitors, at least 3 adult subjects with screening anti-hFVIII inhibitory antibody titers of ≥ 5 Bethesda units (BU) will be enrolled in the study.
Planned Duration of Subject Participation	The duration of subject participation depends on the nature of the invasive procedure: it will run from the signing of the informed consent until completion of the End of Study Visit (at least 5 weeks post-last dose).

Primary Outcome Measure

The primary outcome measure is the proportion of all surgical, dental, or other invasive procedures with a "good" or "excellent" response as measured by GHEA score, which is composed of 3 individual ratings:

- GHEA1: Assessment of intraoperative (Day 0) hemostatic efficacy of BAX 802 performed by the operating surgeon at the end of surgery.
- GHEA2: Assessment of postoperative hemostatic efficacy of BAX 802 at postoperative Day 1 (approximately 24 hours [±6 hours] post-surgery performed by the operating surgeon. If a patient is discharged < 24 hours following surgery, then the GHEA2 hemostatic efficacy assessment may require a return visit the following day.
- GHEA3: Assessment of overall perioperative hemostatic efficacy of BAX 802 at discharge or within 24 to 72 hours after the last perioperative treatment dose of BAX 802 if hospitalization is prolonged for reasons other than perioperative procedures (whichever is earlier), performed by the Investigator, and where possible, also by the operating surgeon. Assessment by both is strongly recommended. In cases where there are differing assessments, the Investigator's assessment will be used.

The scores of each of the 3 individual ratings described above (GHEA1, GHEA2, and GHEA3), will be added together to form a GHEA score. Hemostatic efficacy success is defined as an "excellent" or "good "outcome for ≥ 70% of hemostatic efficacy assessments.

Secondary Outcome Measures

Efficacy

1. Intra- and post-operative blood loss compared to the estimated volume of expected average blood loss and expected maximum blood loss in a comparable healthy individual with similar demographic characteristics as predicted preoperatively by the Investigator/surgeon at the following time points:
   - Intraoperative, from start until the end of surgery
   - Postoperative Day 1, from end of surgery to approximately 24 hours ±6 hours after surgery
   - Overall perioperative at discharge or 24 to 72 hours after the last perioperative treatment dose of BAX 802 (whichever is earlier)
2. Proportion of major surgeries with good or excellent hemostatic outcome together with its 2-sided 95% confidence interval
3. Daily and total weight-adjusted administration of BAX 802 per subject
4. Amount of blood, red blood cells, platelets, and other blood products transfused

Safety

1. Development of, and changes to, the titer of inhibitory and binding antibodies immunoglobulin G (IgG) and immunoglobulin M (IgM) to pFVIII
2. Development of, and changes to, the titer of inhibitory and binding antibodies (IgG and IgM) to hFVIII
3. Development of binding antibodies to BHK proteins
4. Occurrence of thrombo-embolic events
5. Incidence of severe allergic reactions (e.g., anaphylaxis)
6. Incidence of other IP-related AEs
7. Incidence of clinically significant changes in vital signs and routine laboratory parameters (hematology, clinical chemistry)

Exploratory Outcomes Measures

[redacted]

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form:** Injectable reconstituted solution of BAX 802, rpFVIII from which the B domain has been deleted. **Dosage frequency:** Loading dose, followed by subsequent individualized dosing. **Mode of Administration:** Intravenous bolus infusion (to the cubital vein is the recommended anatomical site of administration).
SUBJECT SELECTION	
Targeted Accrual	Enroll approximately 12 evaluable subjects (2 of which will be adolescents ≥ 12 to < 18 years old) for approximately 12 procedures.
Number of Groups/Arms/Cohorts	Single-arm

Inclusion Criteria

1. Subject requires a major or minor elective surgical, dental or other invasive procedure
2. Subject is male and ≥ 12 to ≤ 75 years old at the time of screening
3. Subject has provided signed informed consent (and assent for adolescent subjects, as applicable) in accordance with local regulatory requirements
4. Subject has severe (FVIII level < 1%) or moderately severe (FVIII level ≤ 2%) CHA with inhibitors to human FVIII (hFVIII), of ≥ 0.6 BU, as tested at screening at the central laboratory
5. Subject is not currently receiving or has recently received (< 30 days) immune tolerance induction (ITI) therapy
6. Subject has a Karnofsky performance score of ≥ 60 at screening
7. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm^3 at screening
8. Subject is hepatitis C virus negative (HCV-) by antibody or polymerase chain reaction (PCR) testing; or HCV+ with chronic stable hepatitis disease. (If positive, the antibody titer will be confirmed by PCR.)
9. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

1. The subject requires emergency surgery
2. Severe chronic liver dysfunction or disease (e.g., ≥ 5 × upper limit of normal [ULN] alanine aminotransferase [ALT], as confirmed by central laboratory at screening or a documented prothrombin time/international normalized ratio [PT/INR] > 1.5)
3. Clinically symptomatic renal disease (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening
4. Anti-porcine FVIII (pFVIII) > 10 BU prior to surgery
5. Platelet count < 100,000/µL at screening
6. Subject has another active coagulation disorder, other than hemophilia A, as per the medical history
7. Planned use of α-interferon with or without ribavarin for HCV infected patients or planned use of a protease inhibitor for HIV-infected patients. Patients currently taking any of these medications for ≥ 30 days are eligible
8. Known hypersensitivity to rpFVIII, or hamster or murine proteins
9. Subject has an ongoing or recent (within 3 months of screening) thrombo-embolic disease, fibrinolysis or disseminated intravascular coagulation (DIC).
10. Subject has been exposed to an IP 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
11. Subject is unable to tolerate quantity of blood to be drawn for protocol procedures
12. Subject is a family member or employee of the Investigator

STATISTICAL ANALYSIS

Sample Size Calculation

The sample size of approximately 12 surgeries/procedures in 12 evaluable male subjects (at least 5 major surgeries/procedures in 5 evaluable subjects), as defined in the protocol, was chosen to provide sufficient evidence of safety and effectiveness for this indication and is not based on statistical considerations.

Evaluable subjects are defined as subjects who met all study entry criteria and who had at least 1 hemostatic efficacy assessment.

Planned Statistical Analysis

Analysis Sets

The safety analysis set (SAS) will be comprised of all subjects who received any amount of BAX 802. The full analysis set (FAS) will be comprised of all surgeries with at least 1 available hemostatic assessment. The per-protocol analysis set (PPAS) will be comprised of all surgeries with evaluable ratings for all 3 perioperative hemostatic efficacy assessments, whose subjects met all study entry criteria and had no major protocol violations that might impact hemostatic efficacy assessments.

Primary Outcome Measure

The primary efficacy measure will be the overall assessment of hemostatic efficacy assessed intraoperatively and postoperatively by the surgeon at postoperative Day 1 (postoperative period, i.e., from end of surgery to 24 ±6 hours post-surgery) and perioperatively at 24 to 72 hours after the last perioperative treatment dose of BAX 802 is administered or discharge (whichever is earlier) by the surgeon and by the Investigator, and will be the sum of intraoperative, postoperative, and perioperative GHEA scores rated "excellent", "good", "fair" or "none".

If discharge is delayed for a reason other than surgery related bleeding (e.g., pneumonia), an assessment at 24 to 78 hours after last perioperative treatment dose of BAX 802 will ensure that the overall perioperative assessment is completed close to the last administered study drug dose. Wherever possible (except for intraoperative assessment), bleeding should be assessed by both operating surgeon and Investigator. To achieve the hemostatic efficacy success criteria, the study needs to achieve a ≥ 70% rate of hemostatic efficacy assessments with an "excellent" or "good" outcome in at least 12 procedures.

Due to the possibility of a subject undergoing multiple surgeries, the statistical analysis of the primary outcome measure will be reported on the by-surgery level (i.e., not by the number of subjects). In cases where two or more surgical procedures are performed in the same intraoperative settings (under the same anesthesia, e.g., bilateral knee replacement) the surgery will be counted as one surgery. Blood loss assessment from those surgeries will be assessed as one. In the event that the subject is planning to have additional surgery in the future, the subject will need to complete the study and be re-screened again (if > 3 months from the screening) to ensure that they continue to meet the eligibility criteria.

Point estimates and corresponding 2-sided exact Clopper-Pearson confidence intervals (CIs) at the 95% confidence level will be calculated for the rate of hemostatic efficacy assessments with excellent/good outcome for descriptive purposes.

The proportion of all surgeries and of all major surgeries with hemostatic success will be reported along with exact 95% CIs. A treatment success will be defined as a rating of excellent or good.

The primary efficacy analysis will be based on the FAS population. As a supportive analysis, the same calculations will also be carried out on the PPAS population.

A sensitivity analysis based on the first surgery will be performed if more than 20% of subjects have multiple surgeries.

Any blood loss which is considered as unrelated bleeding (defined as any bleeding occurring at a different anatomical site other than the surgery site during the postoperative period) will not be taken into account for while making assessment of hemostatic efficacy for the primary efficacy measure.

Secondary Outcome Measures

Secondary hemostatic efficacy analysis:

Secondary outcome measures will be reported at the surgery level rather than the subject level. Descriptive statistics will be used to summarize the actual blood loss and transfusion requirements. The proportion of major surgeries with good or excellent hemostatic score together with its 2-sided 95% CI will be reported for descriptive purposes.

The summary of average daily and total weight-adjusted doses (average through postoperative 24 to 72 hours after last perioperative treatment dose of BAX 802 or discharge [whichever is earlier]) of BAX 802 per subject as well as the occurrence of bleeding episodes will be provided using descriptive statistics.

For unrelated bleeding episodes in the postoperative period, descriptive statistics will be used to summarize the overall hemostatic efficacy rating at 24 ±2 hours after initiation of treatment and at resolution of bleed (if not resolved within 24 hours). The secondary efficacy analysis will be performed on the FAS only. Separate descriptive summaries of average daily and total weight-adjusted doses required to treat unrelated bleeding episodes and will be provided.

Safety Analysis

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by presenting the number and proportion of subjects having any AE, having an AE in each system organ class, and having each individual AE as reported by preferred term. In the summaries, AEs will be counted only once per patient. If a patient reports the same AE more than once, it will be counted with its worst severity and closest relationship to the study product.

The number of subjects who experienced SAEs and the number of SAEs will be tabulated. In addition, the number of subjects who experienced AEs related to IP and the number of IP related AEs will be tabulated and subcategorized for thrombo-embolic events, inhibitory and total binding antibodies (IgG and IgM) to rpFVIII and hFVIII, and binding antibodies to BHK proteins.

An overview table for AEs will be provided, presenting the number of AEs, the number of subjects with AEs and the corresponding percent of subjects in total, and by seriousness and relationship to study treatment. An additional summary table will present the total number of (mild, moderate, severe) AEs by system organ class and preferred term with relationship to IP.

Summary statistics over time will be presented for the continuous laboratory parameters. Descriptive statistics of changes from baseline (prior to BAX 802 loading dose before the surgery) by study visits will also be presented.

A frequency table of results of categorical laboratory parameters will be produced. Furthermore, laboratory abnormalities will be analyzed by shift tables where each subject will be counted only once with the worst grade in the summary tables.

Vital signs assessments as well as the corresponding changes from baseline will be summarized descriptively at each scheduled or unscheduled assessment.

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AHA	acquired hemophilia A
AICC	anti-inhibitor coagulant complex
ALT	alanine aminotransferase
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
B19V	parvovirus B19
BHK	baby hamster kidney
BU	Bethesda units
CI	confidence interval
CHA	Congenital Hemophilia A
CRF	case report form
CTA	Clinical Trial Agreement
DIC	disseminated intravascular coagulation
DSMB	data safety monitoring board
EBL	estimated blood loss
EC	Ethics Committee
ELISA	enzyme-linked immunosorbent assay
EU	European Union
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FVIII	Factor VIII
GCP	Good Clinical Practice
GHEA	Global Hemostatic Efficacy Assessment
HAV	hepatitis A virus
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
HEV	hepatitis E virus
hFVIII	human factor VIII
HIV	human immunodeficiency virus

Abbreviation	Definition
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG	immunoglobulin G
IgM	immunoglobulin M
IP	investigational product
IPC	intermittent pneumatic compression
IRB	Institutional Review Board
ITI	immune tolerance induction
ITT	intent-to-treat
LMWH	low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
NMC	Non-medical complaint
OR	operating room
PCR	polymerase chain reaction
pFVIII	porcine factor VIII
PK	pharmacokinetics
PPAS	per protocol (analysis set)
PT/INR	prothrombin time/international normalized ratio
PV	plasma volume
rhFVIII	recombinant human factor VIII
rpFVIII	recombinant porcine factor VIII
RSI	Reference Safety Information
SAE	serious adverse event
SAER	serious adverse event report
SAP	statistical analysis plan
SAS	safety analysis set
SIC	subject identification code
SOC	standard of care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	thrombin generation assays
U	unit(s)
ULN	upper limit of normal
US	United States
US CFR	US Code of Federal Regulations
VIIa	activated factor VII
WFH	World Federation of Hemophilia

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

The investigational product (IP), BAX 802, is a recombinant form of porcine factor VIII (rpFVIII) from which the B domain has been deleted. Deletion of the B domain does not affect the safety or efficacy of this recombinant form of human factor VIII (rhFVIII) in the treatment of hemophilia A. BAX 802 (rpFVIII) is being developed for the perioperative management of hemostasis in subjects with congenital hemophilia A (CHA) with inhibitors to human factor VIII (hFVIII) undergoing surgical or other invasive procedures. This rpFVIII was approved by the United States Food and Drug Administration (FDA) in 2014 for the treatment of bleeding episodes in adults with acquired hemophilia A (AHA; non hemophilia subjects developing spontaneous autoantibody inhibitors to hFVIII) under the trade name OBIZUR®.

6.2 Clinical Condition/Indication

Congenital hemophilia A is a congenital bleeding disorder caused by a deficiency or complete absence of coagulation factor VIII (FVIII) [1] and is referred to as CHA in order to differentiate it from AHA, which is a rare autoimmune disease with different bleeding patterns caused by immunoglobulin G antibodies that bind to specific domains on the FVIII molecule, in a person with a negative personal or family history of a coagulopathy.[2]

Overall, CHA accounts for about 80% of hemophiliacs. It affects all ethnic populations and its prevalence varies among different countries, but is estimated at a rate of 3 to 20 cases per 100,000 population. The World Federation of Hemophilia (WFH) has estimated the total number of hemophilia cases at about 500,000 worldwide, of which one-third are diagnosed. The tendency to bleed in these subjects correlates with the plasma level of FVIII. This lifelong disorder has 3 clinical phenotypes (severe, moderate, and mild) that correlate with FVIII levels in plasma (< 1%, 1 to 5%, and 5 to 40%, respectively).[3]

Subjects with hemophilia A typically develop recurrent bleeding episodes. The most effective approach for treatment of acute bleeding episodes in subjects with hemophilia A is hFVIII replacement therapy.[4,5] However, a major complication in the treatment of subjects with hemophilia A is the development of neutralizing antibodies (inhibitors) to hFVIII, which impair the efficacy of replacement therapy with hFVIII concentrates. Inhibitor development occurs more frequently among patients with severe or moderately severe hemophilia, and approximately 30% of patients with severe CHA develop inhibitors. In CHA patients with high-responding inhibitors, standard replacement

therapy with FVIII concentrates is usually ineffective, resulting in poor control of hemorrhagic episodes. This, in turn, increases the risk of morbidity, mortality, orthopedic complications and disability, as well as reduced quality of life, compared with patients without inhibitors.[6] Patients with CHA with inhibitors are also at risk of perioperative bleeding complications, since replacement of the missing coagulation factor is ineffective, presenting a therapeutic challenge in elective or emergency surgery.[7]

Currently Available Treatments and Unmet Medical Need

In CHA patients with transient, low-responding, and/or low-titers (< 5 Bethesda units [BU]/mL) inhibitors, increased doses of FVIII may be sufficient to overcome the inhibitor and provide hemostasis. In CHA patients with high-responding inhibitors (> 5 BU/mL), standard replacement therapy with FVIII concentrates is usually ineffective, resulting in poor control of hemorrhagic episodes.

Alternative therapies are required for subjects with inhibitors who no longer respond to hFVIII replacement therapy. Recombinant activated factor VII (rFVIIa, NovoSeven®) and FEIBA (FVIII inhibitor bypassing activity; anti-inhibitor coagulant complex [AICC]) bypass the normal coagulation cascade and hence the FVIII inhibitors, and are therefore referred to as bypassing agents. Although these agents are able to manage bleeding in the presence of inhibitors, they do not attempt to restore the normal pathways of hemostasis, but instead boost thrombin generation despite a lack of platelet-surface FVIIIa–FIXa ('tenase') activity.[6] The measurement of levels of factor VIIa in the subject's plasma cannot be used as a clinically relevant surrogate marker and does not correlate with clinical outcome. Without an adequate biomarker, the dosage and treatment schedule cannot be clearly defined.[8] In addition, the response to rFVIIa treatment may be inconsistent both from subject to subject and between different bleeds in the same subject. Because FEIBA is a human plasma fraction containing several coagulation factors, it has the potential to transmit human pathogens and may also cause thromboembolic events. Since the plasma fraction also contains hFVIII, it has been associated with a rise in hFVIII antibodies in approximately 20% of subjects.[9] Moreover, as with rFVIIa, there is no validated biomarker that correlates with the clinical outcome with FEIBA treatment, although both thrombin generation assays (TGA) and whole blood viscoelastic assays have been evaluated for this purpose with some success.[10]

The ultimate goal of treatment for these patients is eradication of the inhibitor through immune tolerance induction (ITI), which involves frequent and long-term administration of factor concentrates in an attempt to build tolerance in the immune system to FVIII or factor IX, and thus restore responsiveness to factor replacement therapy. However, ITI fails in approximately 30% of inhibitor patients with CHA.[6]

There is therefore a clinical need for an effective hemostatic agent for use in subjects with CHA who have inhibitors to hFVIII, and which allows monitoring of hemostatic efficacy based upon measurement of plasma FVIII activity levels, thus facilitating early determination of clinical benefit and the patient's clinical status.

6.3 Population to be Studied

The study population will comprise of at least 12 procedures in 12 evaluable male subjects with CHA with inhibitors to hFVIII undergoing major or minor elective surgical, dental, or other invasive procedures (of which no more than 20% can be dental or other non-operative invasive procedures). Of 12 evaluable subjects, at least 2 will be adolescents (≥ 12 to < 18 years old), and in total there will be at least 5 major surgeries in 5 evaluable subjects. Subjects will be considered to be eligible provided that they satisfy all of the inclusion criteria listed in Section 9.1 and none of the exclusion criteria listed in Section 9.2. In order to evaluate the activity of the product with respect to high-titer or high-responding inhibitors to hFVIII, at least 3 adult subjects with screening anti-hFVIII inhibitor titers of ≥ 5 BU will be enrolled in the study.

6.4 Findings from Nonclinical and Clinical Studies

6.4.1 Finding from Nonclinical Studies

Nonclinical studies were performed with rpFVIII to demonstrate hemostatic activity in 2 animal models of hemophilia A (mice and dogs), local and systemic tolerance in a range of doses in single or repeat dose toxicology studies in monkeys, pharmacokinetics (PK) in dogs and monkeys, and immunogenicity in mice and monkeys.

Compatibility with the usual injection materials (needles, plastic syringes, and butterfly infusion needles with tubing) has been demonstrated. Studies in monkeys demonstrated the tolerability of repeated single daily injections of rpFVIII at doses up to 1000 U/kg, with injections at each dose level given once daily for 7 days. In 2 animal models of hemophilia A (mice and dogs), the hemostatic activity of rpFVIII was studied in comparison with Hyate:C. The rpFVIII was found to be efficacious in a dose-related fashion in controlling the bleeding associated with a standardized hemorrhagic insult. No animal studied was observed to have had an acute reaction to the injection of rpFVIII.

6.4.2 Findings from Clinical Studies

The safety and efficacy of rpFVIII was explored in 4 clinical trials prior to marketing approval:

- OBI-1-101 (N=9): a Phase 1, multicenter, randomized, double-blinded, double-dummy, parallel-group, comparison of the safety, tolerance, and PK study of rpFVIII versus Hyate:C was conducted.[11]
- OBI-1-201 (N=9): a Phase 2, prospective, open-label, non-comparative study was conducted to assess the hemostatic activity of rpFVIII. Eligible subjects had a clinical diagnosis of hemophilia A with inhibitors to hFVIII, an anti-pFVIII inhibitor antibody titer < 20 BU at screening, and an uncomplicated joint or soft tissue bleed, or other non-life threatening and non-limb threatening bleeding episode.[12]
- OBI-1-301 (N=29): a multicenter, open-label, single-cohort, prospective, Phase 2/3 study of rpFVIII in subjects with acquired hemophilia to determine the hemostatic efficacy and safety of rpFVIII in the control of serious bleeding episodes.[13]
- OBI-1-302 (terminated at N=1): a prospective, non-randomized, open-label study designed to assess treatment of serious bleeding episodes with rpFVIII in subjects with CHA who had developed anti-hFVIII inhibitors; this study was terminated by the sponsor after 1 subject was treated for administrative reasons, not due to safety or lack of efficacy concerns.

In all clinical studies, rpFVIII was generally well tolerated. There were no drug-related AEs reported in subjects who received rpFVIII in the Phase 1 study. One subject in the Phase 2 study (OBI-1-201) experienced pruritus (that resolved with diphenhydramine) that was possibly related to study drug. This AE occurred during the first bleeding episode, but the subject did not have a reaction during a second rpFVIII treated bleeding episode. In the Phase 1 and Phase 2 studies, no AEs led to treatment interruption, discontinuation from the study, or death. Vital signs, laboratory values, medical history and physical examination findings were within normal parameters for both studies and raised no safety concerns.

In the Phase 2 study (OBI-1-201), the intent-to-treat (ITT) population consisted of 9 male subjects with CHA and with an inhibitor antibody to hFVIII. Six of the subjects (67%) were black and 3 subjects (33%) were Caucasian. The mean age of the subject population was 23.7 years (range: 14 to 34). The primary efficacy objective of the study was to evaluate the hemostatic efficacy of rpFVIII in the treatment of non-life/non-limb threatening bleeds in subjects with CHA and inhibitors.

A total of 25 bleeds in 9 subjects were treated with rpFVIII and all bleeds were successfully controlled with 8 or less injections of rpFVIII. The median number of rpFVIII injections administered per bleeding episode was 1.0 (range: 1 to 8) and the median time from bleeding onset to treatment was 5.67 hours (range: 1.5 to 20.0). Across all bleeding episodes the median total dose of rpFVIII per bleeding episode was 224.1 U/kg (range: 50.0 to 1066.4). The median initial Treatment Dose (including the loading dose if applicable), was 159 U/kg (range: 50 to 576) and resulted in a median increase of FVIII plasma level of 16 % with the 1-stage clotting assay (range: 0.5% to 427%) and a median increase of 17% with the chromogenic assay (range: 0% to 248%). Twenty of the 25 (80%) bleeds were controlled within 6 hours having been administered 1 Treatment Dose of rpFVIII. For those 20 bleeds controlled with 1 Treatment Dose (including the loading dose if applicable), the median dose was 200.8 U/kg. The rpFVIII was well tolerated and of the reported AEs (n=61) only 18 AEs were considered treatment emergent. Two subjects reported an AE that was possibly related to study drug. One AE of itching/pruritus during the first bleeding episode but without reaction during a second rpFVIII treated bleeding episode. The second AE was a report of increased ALT and aspartate aminotransferase (AST), possibly associated with a confirmed hepatitis C infection, while it was uncertain whether the corresponding blood sample was taken before or after rpFVIII administration. Three subjects suffered treatment emergent SAEs but none were considered related to study drug. No reported AE led to treatment interruption, discontinuation from the study or death. Eight out of 9 (8/9, 89%) subjects developed anti-pFVIII antibodies following exposure to rpFVIII. In subjects who received repeated rpFVIII treatment, higher anti-pFVIII titers did not affect efficacy or safety and no increase in AEs or bleeding episodes were reported in the subjects with the highest titers. Regardless of the observed anti-pFVIII titers at pre-treatment or the obtained FVIII recovery values after treatment initiation, all bleeding episodes were successfully controlled. Analyses of baby hamster kidney (BHK; host cell line) antibody levels indicated that no subjects produced detectable levels of antibodies against BHK.

In the prospective, open-label trial (OBI-1-301), the efficacy of rpFVIII for the treatment of serious bleeding episodes in subjects with AHA was investigated. The trial was conducted in 18 Caucasian, 6 African-American, and 5 Asian subjects diagnosed with AHA, having auto-immune inhibitory antibodies to hFVIII, and experiencing serious bleeding episodes that required hospitalization. Subjects with a prior history of bleeding disorders other than AHA, anti-pFVIII antibody titer > 20 BU, or in whom the bleeding episode was judged likely to resolve on its own, were excluded. One subject was considered evaluable at study entry; however, it was later determined that this subject did not have AHA, leaving 28 subjects evaluable for efficacy. Of the 28 subjects evaluable for efficacy, all subjects had a positive response to treatment for the initial bleeding

episodes at 24 hours after dosing. A positive response was observed in 95% (19/20) of subjects evaluated at 8 hours and 100% (18/18) at 16 hours. In addition to response to treatment, the overall treatment success was determined by the Investigator based on his/her ability to discontinue or reduce the dose and/or dosing frequency of rpFVIII. A total of 24/28 subjects (86%) had successful treatment of the initial bleeding episode. Of those subjects treated with rpFVIII as first-line therapy, defined as no immediate previous use of anti-hemorrhagic agents prior to the first rpFVIII treatment, 16/17 subjects (94%) had eventual treatment success reported. Eleven subjects were reported to have received anti-hemorrhagics (eg, rFVIIa, activated prothrombin-complex concentrate, and tranexamic acid) prior to first treatment with rpFVIII. Of these 11 subjects, 8 had eventual successful treatment (73%). No related serious adverse reactions occurred. Non-serious AEs related to treatment were noted and assessed by the Investigator in 6/29 subjects (20.7%). One subject had mild tachycardia, hypotension and constipation. One subject had 2 instances of mild peripherally inserted central catheter (PICC) line occlusion. One subject had a mild hypofibrogenemia and 1 subject had moderate mental status changes. All of these adverse effects completely resolved. Two subjects developed anti- pFVIII inhibitors after infusion of study drug (range 8 to 51 BU) and were discontinued from treatment; however both subjects had a positive response to treatment at the 24-hour primary endpoint assessment. An investigation was conducted by the sponsor and, in summary, the 2 incidences of anti-pFVIII inhibitors were considered related to rpFVIII treatment, while the other non-serious treatment-related adverse events were considered as unlikely to be related to rpFVIII. Anti-pFVIII inhibitors were detected prior to infusion in 10/29 patients (range 0.8 to 29 BU). All of these subjects had a positive response at 24 hours post-rpFVIII first infusion. No anti-BHK antibodies were observed in any of the 29 treated subjects.

At the time of OBIZUR® marketing approval, the clinical trial data indicated that rpFVIII was well tolerated and had demonstrated effectiveness in the control of bleeding in study subjects. Cumulatively (patient exposure from 01 Oct 2014 through 31 Oct 2016), approximately 16,424,000 units (U) of OBIZUR® were sold worldwide. Median (range) treatment dose per bleeding episode was 94,500 (35,256 to 182,700), and the estimated number of patient-years worldwide to OBIZUR® was approximately 347.6 (179.8 to 931.6). As of 11 Nov 2016, there have been 20 post-marketing serious case reports with 36 AEs. No adverse reactions other than those observed in clinical trials have been observed in the post marketing setting. The reports were consistent with the known safety profile of OBIZUR®.[i]

[i] Obizur Periodic Safety Update Report/Periodic Benefit-Risk Evaluation Report (PSUR/PBRER), reporting interval 12 MAY 2016 to 11 NOV 2016.

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

Porcine FVIII (Hyate:C), derived from porcine plasma, had been used successfully starting in the 1980s to achieve hemostasis in the presence of anti-hFVIII inhibitors, as the antibodies generally have low immunological cross-reactivity with pFVIII.[14] However, the number of hemophilia A subjects who were appropriate candidates to receive Hyate:C was limited by the degree to which their anti-hFVIII antibodies cross-reacted with pFVIII and the presence of any anti-pFVIII inhibitors. While a median inhibitor cross-reactivity observed to porcine VIIIC was only 15%, an absent, intermediate, or brisk specific anti-porcine anamnestic response was observed in 29%, 40%, and 31% of patients, respectively.[15] The commercial production of Hyate:C was discontinued in 2005 due to problems with sourcing suitable porcine plasma, but not due to any safety or efficacy concerns.

BAX 802 is a B-domain deleted rpFVIII glycoprotein which is being developed for the perioperative management of hemostasis in subjects with CHA with FVIII inhibitors undergoing surgical or other invasive procedures. B-domain deleted rpFVIII glycoprotein has been extensively studied. BAX 802 (as marketed OBIZUR®) is not currently indicated for the treatment of CHA.[16]

OBIZUR® was approved based on the safety and efficacy data from 28 subjects with AHA treated with B-domain deleted rpFVIII glycoprotein in the Phase 2/3 open-label clinical study OBI-1-301. The safety, hemostatic activity, and PK profile of B-domain deleted rpFVIII glycoprotein was also supported by results of an open-label Phase 2 study in patients with CHA with inhibitors (Clinical Study Report OBI-1-201), and a randomized Phase 1 study comparing B-domain deleted rpFVIII glycoprotein with a plasma-derived pFVIII (CSR OBI-1-101).

The data supported the use of B-domain deleted rpFVIII glycoprotein to treat serious bleeding episodes in AHA patients (Section 6.4.2). It was demonstrated that B-domain deleted rpFVIII glycoprotein provides benefit to AHA patients who are unresponsive to alternative agents with an improved dosing algorithm. It was possible to monitor hemostatic efficacy based upon measurement of plasma FVIII activity levels, thus facilitating early determination of clinical benefit and the patient's clinical status. An additional benefit to the patient was that it was possible to adjust the dose based on the FVIII levels rather than follow fixed dosing, ensuring that adequate doses were administered to achieve hemostasis.

The most frequently reported adverse reaction in patients with AHA was the development of inhibitors to pFVIII.[16]

Overall, efficacy and safety clinical data for OBIZUR supported a favorable benefit/risk determination for the proposed indication of treatment of bleeding episodes in adults with AHA.

These data support the investigation of efficacy and safety of BAX 802 in subjects with CHA with inhibitors undergoing surgical or other invasive procedures.

6.6 Compliance Statement

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

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is to evaluate the efficacy and safety of BAX 802 in males with CHA with inhibitors who are undergoing major or minor elective surgical, dental, or other invasive procedures.

7.2 Primary Objective

The primary objective of the study is to evaluate the perioperative hemostatic efficacy of BAX 802 in male subjects with CHA with inhibitors to hFVIII undergoing major or minor elective surgical, dental, or other invasive procedures as determined by the Global Hemostatic Efficacy Assessment (GHEA) score.

7.3 Secondary Objectives

The secondary objectives of the study are:

1. To determine the safety of BAX 802 used in the perioperative setting by assessing:
    - The development of and change in titer of anti-pFVIII and anti-hFVIII antibodies (binding and neutralizing), and development of binding antibodies to BHK proteins
    - The occurrence of thrombo-embolic events and/or allergic reactions to BAX 802
    - The occurrence of AEs related to BAX 802
    - The occurrence of clinically significant changes in vital signs and routine laboratory parameters related to BAX 802
2. To determine the intraoperative, postoperative, and overall perioperative blood loss, compared to the estimated volume of expected average and maximum blood loss in a comparable healthy individual as predicted preoperatively by the Investigator/surgeon
3. To determine the proportion of major surgeries with good or excellent hemostatic score
4. To determine the daily and total weight-adjusted administration of BAX 802 per subject

7.4 Exploratory Objectives

The exploratory objectives of the study are:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

8. STUDY DESIGN

8.1 Brief Summary

This study is a Phase 3, prospective, single-arm, open-label, uncontrolled, multicenter study to evaluate the efficacy and safety of BAX 802 in at least 12 procedures in 12 evaluable male subjects ≥ 12 to ≤ 75 years old with CHA with inhibitors to hFVIII who are undergoing major and minor surgical, dental or other invasive procedures. At least 5 of the procedures must be major surgeries in 5 evaluable subjects, of which no more than 20% can be dental or other non-operative invasive procedures (see Section 8.2.1), and at least 3 adult subjects with screening anti-hFVIII titers of ≥ 5 BU for inhibitors to human FVIII will be enrolled in the study. At least 2 adolescents (≥ 12 to < 18 years old) will be enrolled in the study.

8.2 Overall Study Design

The dose and frequency of BAX 802 during the preoperative, intraoperative, and postoperative periods should follow a proposed substitution plan provided by the Investigator to the medical monitor prior to surgery and adjusted based on regular FVIII activity measurements (see Section 8.7.3.1). The regimen will depend on the type of surgery performed and the intensity of the hemostatic challenge.

Elective surgical procedures will prospectively be defined as major or minor by the Investigator/surgeon and agreed with the medical director/designee, based on the protocol guidance and definitions and in consideration of each subject's characteristics. Emergency surgeries are not in the scope of this study. Subjects may undergo more than 1 surgery or 2 parallel surgeries, such as bilateral knee replacement. For subjects undergoing multiple surgeries (other than parallel surgeries), the End of Study visit should be completed for the first surgery and then subject needs to be re-screened (Section 10.3) for the next surgery.

The study will be divided into 5 periods: Screening, Preoperative, Intraoperative, Postoperative, and End of study (Table 8). The study will be conducted at multiple sites in North America, Europe, and South Africa.

The overall study design is illustrated in Figure 2.

8.2.1 Types of Interventions

Elective surgeries and other invasive procedures will prospectively be defined by the Investigator/surgeon as major or minor based on the definitions and examples provided in Section 8.2.1.1 and Section 8.2.1.2, respectively, taking into consideration each individual patient's characteristics and agreement with the sponsor.

8.2.1.1 Major Surgeries

Major surgeries include surgeries that require moderate or deep sedation, general anesthesia, or major conduction blockade for patient comfort. This generally refers to major orthopedic (e.g., joint replacement), major abdominal, intracranial, cardiovascular, spinal and any other surgery which has a significant risk of large volume blood loss (> 500 mL) or blood loss into a confined anatomical space. Extraction of at least 3 teeth or extraction of the third molar are generally considered as major. Examples include:

- bone fixation for fracture
- hip and knee replacement (arthroplasty)
- arthrodesis (joint fusion)
- open synovectomy
- osteotomy
- liver biopsy
- pseudotumor removal
- hardware removal (plates and intramedullary nails)

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

8.2.1.2 Minor Surgeries

Minor surgeries include surgeries that can be safely and comfortably performed on a patient who has received local or topical anesthesia, without more than minimal preoperative medication or minimal preoperative medication or minimal intraoperative sedation. The estimated total blood loss should be < 500 mL and the likelihood of complications requiring hospitalization or prolonged hospitalization should be remote. It refers to interventions such as removal of skin lesions, arthroscopy, minor dental procedures or dental extractions. Examples include:

- removal of skin lesions
- minor dental procedures or dental extractions (except extraction of 3 or more teeth or third molar extraction)
- placement and/or removal of central venous catheters
- synoviorthesis and arthrocentesis

- arthroscopy
- 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

8.2.2 Dose Selection Rationale

Background

This is a Phase 3, multicenter, single-arm, open-label study of the efficacy and safety of B-domain deleted rpFVIII (BAX 802) in the perioperative management of hemostasis in subjects with CHA who have inhibitors and are undergoing surgical or other invasive procedures. The rpFVIII temporarily replaces the inhibited FVIII that is needed for effective hemostasis in CHA patients who have developed inhibitors to hFVIII. The principle of using pFVIII is based on its low cross-reactivity with anti-hFVIII antibodies due to sequence variations between human and pFVIII in the A2 and C2 domains, the main targets of FVIII inhibitors. The rpFVIII concentrate is predicted to have an advantage over human-derived FVIII in CHA patients who have inhibitors since previous studies demonstrated that the antibodies have a median of only 15% cross-reactivity with plasma-derived pFVIII.[17]

Regulatory approval for rpFVIII for the treatment of bleeding episodes in adults with AHA was received for OBIZUR®; per the product label, the initial dose of OBIZUR® is 200 U/kg, with subsequent dosing dependent on the location and severity of bleeding episode, target FVIII levels, and the patient's clinical condition.[16]

Influence of Anti-pFVIII Inhibitor Titer on the Loading Dose

Anti-pFVIII inhibitors are neutralizing antibodies against pFVIII that neutralize the pFVIII, and thereby reduce its hemostasis effect. Anti-pFVIII inhibitors can be quantified in plasma by the Bethesda assay, which measures the ability of the patient's plasma to neutralize exogenous pFVIII when incubated together.

The amount of BAX 802 required to neutralize the anti-pFVIII activity is factored in. A BU is defined as the amount of anti-pFVIII inhibitor in a plasma sample which will neutralize 50% of 1 unit of BAX 802 in normal plasma after 2 hour incubation at 37°C.

Only the inhibitor that is distributed in the plasma volume (PV) is initially available to neutralize the infused FVIII; PV is calculated using the following formula:

$$PV = \text{Blood Volume} \times (1 - [\text{hematocrit}\{HCT\}\%/100])$$

Normal blood volume is approximately 80 mL/kg for adults.

Therefore, $PV = 80 \times (1 - [HCT\%/100])$.

One BU of anti-pFVIII inhibitor will neutralize 50% of 1 unit of BAX 802; therefore, it is assumed that 0.5 U FVIII will be required for each 1 BU of inhibitor. The amount of BAX 802 required to neutralize the anti-pFVIII activity can be estimated using the following:

$$\text{Body weight} \times 80(1 - [HCT\%/100]) \times 0.5 \times \text{anti-pFVIII inhibitor titer (BU)} = \text{body weight} \times 40(1-[HCT\%/100]) \times \text{anti-pFVIII inhibitor titer (BU)}.$$

Proposed Dosing Regimen of BAX 802 in Study BAX 802 Surgery

The dosing scheme to be used in Study BAX 802 Surgery is presented in Section 8.7.3.3.

The loading dose of BAX 802 for a CHA subject with inhibitors undergoing major surgery is calculated using the following formula:

$$[80 \times \text{body weight (kg)}] + [\text{body weight (kg)} \times 40(1-[HCT\%/100]) \times \text{anti-pFVIII inhibitor titer (BU)}]$$

For example, for a 70 kg subject undergoing major surgery and having HCT 45% and anti-pFVIII inhibitor titer 3 BU, the loading dose of BAX 802 will is calculated as follows:

$$[80\ (70)] + [70 \times 40(1-[45/100]) \times 3] = 10{,}220\ \text{U}$$

This dosing scheme should reasonably predict the loading dose before surgery that will provide sufficient FVIII levels needed for effective hemostasis.

Subsequent doses, dosing frequency, and duration of treatment will be based on clinical judgment and measured FVIII levels achieved, and will require empirically based adjustments until hemostasis is achieved (Table 5).

This dosing algorithm is essentially equivalent to that proposed by Kasper (2004) when using FVIII in the treatment of patients with low titer inhibitors.[18]

8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study will be approximately 21 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject, last visit). The recruitment period is expected to be approximately 18 months.

The duration of subject participation depends on the nature of the invasive procedure: it will run from the signing of the informed consent until completion of the End of Study Visit at least 5 weeks post-surgery (end of surgery = Day 0), unless prematurely discontinued. Study completion is defined by the End of Study Visit after discharge.

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

The primary outcome measure is the proportion of all surgical, dental, or other invasive procedures with a "good" or "excellent" response as measured by GHEA score (Table 1), which is composed of 3 individual ratings:

- GHEA1: Assessment of intraoperative (Day 0) hemostatic efficacy of BAX 802 performed by the operating surgeon (see Table 2) at the end of surgery
- GHEA2: Assessment of postoperative hemostatic efficacy of BAX 802 at postoperative Day 1 (approximately 24 hours [± 6 hours] post-surgery) performed by the operating surgeon. If a patient is discharged < 24 hours following surgery, then the GHEA2 hemostatic efficacy assessment may require a return visit the following day (see Table 3)
- GHEA3: Assessment of overall perioperative hemostatic efficacy of BAX 802 at discharge or within 24 to 72 hours after the last perioperative treatment dose of BAX 802 (whichever is earlier), performed by the Investigator, and where possible, also by the operating surgeon. Assessment by both is strongly recommended. In cases where there are differing assessments, the Investigator's assessment will be used (see Table 4)

Prior to the surgery, the surgeon/Investigator will predict the estimated volume (in mL) of the expected 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 and from completion of the procedure until approximately 24 hours post-surgery and for the overall perioperative period (see Section 11.2.1).

The scores of each of the 3 individual ratings (GHEA1, GHEA2, and GHEA3) described above, will be added together to form a GHEA score according to Table 1. For a GHEA score of 7 to be rated "excellent" no individual assessment score should be less than 2 (i.e., one individual assessment score must be 3 and the other two individual assessment scores must be 2). The only other option to achieve a GHEA score of 7 is for two individual assessment scores of 3 and one individual assessment score of 1. Although this GHEA score will not qualify for a rating of "excellent," the GHEA score will satisfy the definition of "good," (with no individual assessment score less than 1). All possible combinations of the individual assessment scores and their related ratings are provided in Supplement Section 20.5.

For surgeries with up to 2 missing hemostatic assessments that did not necessitate rescue therapies, the rating of "fair" will be imputed for these missing data. These surgeries will be included in the full analysis set (FAS). The assessment of primary outcome measure (GHEA score) should only account for the blood loss related to the surgery and exclude any blood loss which is considered as unrelated bleeding (defined as any bleeding occurring at a different anatomical site than the surgery site during the postoperative period, see Section 11.2.5).

Table 1: Global Hemostatic Efficacy Assessment (GHEA)

Assessment	GHEA Score
Excellent	7[a] to 9 (with no category scored < 2)
Good	5 to 7[a] (with no category scored < 1)
Fair	3 to 4 (with no category scored < 1)
None	0 to 2 (or at least one category scored 0)

[a] For a GHEA score of 7 to be rated "excellent" (with no individual assessment scores less than 2), at least 1 individual assessment score must be 3 and the other 2 individual assessment scores must be at least 2; otherwise a score of 7 is rated "good".

Table 2: Intraoperative Efficacy Assessment Scale (GHEA1)

	At the end of surgery, the operating surgeon will assess the intraoperative hemostatic efficacy	
Rating	**Criteria**	**Score**
Excellent	Intraoperative blood loss was less than or equal to that expected for the type of procedure performed in a non-hemophilic population (≤ 100%)	3
Good	Intraoperative blood loss was up to 50% more than expected for the type of procedure performed in a non-hemophilic population (101 to 150%)	2
Fair	Intraoperative blood loss was more than 50% of that expected for the type of procedure performed in a non-hemophilic population (> 150%)	1
None	Uncontrolled hemorrhage that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy or other FVIII products	0

Table 3: Postoperative Efficacy Assessment Scale (GHEA2) (Postoperative Day 1)

	On postoperative Day 1 (24 ± 6 hours post-surgery), the operating surgeon will assess the postoperative hemostatic efficacy	
Rating	**Criteria**	**Score**
Excellent	Postoperative blood loss was less than or equal to (≤ 100%) that expected for the type of procedure performed in a non-hemophilic population	3
Good	Postoperative blood loss was up to 50% more (101% to 150%) than expected for the type of procedure performed in a non-hemophilic population	2
Fair	Postoperative blood loss was more than 50% (> 150%) of that expected for the type of procedure performed in a non-hemophilic population	1
None	Significant postoperative bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy or other FVIII products	0

Table 4: Overall Perioperative Efficacy Assessment Scale (GHEA3) (at Discharge or Within 24 to 72 hours after the last perioperative treatment dose of BAX 802 [whichever is earlier])

	At discharge or within 24 to 72 hours after the last perioperative treatment dose of BAX 802 (whichever is earlier), the postoperative efficacy assessment will be performed by the Investigator, and where possible, also by the operating surgeon	
Rating	**Criteria**	**Score**
Excellent	Overall perioperative blood loss was less than or equal to (≤ 100%) that expected for the type of procedure performed in a non-hemophilic population, Required blood components for transfusions were less than or similar to that expected in non-hemophilic population	3
Good	Overall perioperative blood loss was up to 50% more (101% to 150%) than expected for the type of procedure performed in a non-hemophilic population Required blood components for transfusions were less than or similar to that expected in non-hemophilic population	2
Fair	Overall perioperative blood loss was more than 50% of that expected for the type of procedure performed in a non-hemophilic population (> 150%) Required blood components transfusions were greater than that expected in non-hemophilic population	1
None	Significant overall perioperative bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy or other FVIII products Required blood components for transfusions were substantially greater than that expected in non-hemophilic population	0

Hemostatic efficacy success is defined as "excellent" or "good "outcome for ≥ 70% of hemostatic efficacy assessments.

8.4.2 Secondary Outcome Measures

8.4.2.1 Efficacy

1. Intra- and post-operative blood loss compared to the estimated volume of expected average blood loss and expected maximum blood loss in a comparable healthy individual with similar demographic characteristics as predicted preoperatively by the Investigator/surgeon at the following time points:
    - Intraoperative, from start until the end of surgery
    - Postoperative Day 1, from end of surgery to approximately 24 hours (± 6 hours) after surgery
    - Overall perioperative at discharge or 24 to 72 hours after the last perioperative treatment dose of BAX 802 (whichever is earlier)

2. Proportion of major surgeries with good or excellent hemostatic score
3. Daily and total weight-adjusted administration of BAX 802 per subject
4. Amount of blood, red blood cells, platelets, and other blood products transfused

8.4.2.2 Safety

1. Development of, and changes to, the titer of inhibitory and binding antibodies (IgG and IgM) to pFVIII
2. Development of, and changes to, the titer of inhibitory and binding antibodies (IgG and IgM) to hFVIII
3. Development of binding antibodies to BHK proteins
4. Occurrence of thrombo-embolic events
5. Incidence of severe allergic reactions (e.g., anaphylaxis)
6. Incidence of other IP-related AEs
7. Incidence of clinically significant changes in vital signs and routine laboratory parameters (hematology, clinical chemistry)

8.4.3 Exploratory Outcome Measures

[redacted]

8.5 Randomization and Blinding

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

8.6 Study Stopping Rules

The study will be halted (enrollment stopped), pending further review by the external data safety monitoring board (DSMB) and sponsor, if 1 or more of the following criteria are met:

1. Two or more subjects develop a severe anaphylactic reaction or any other serious adverse event (SAE) related to BAX 802 that would not be expected
2. The occurrence of Suspected Unexpected Serious Adverse Reaction (SUSAR)
3. Other AEs that are deemed to pose unacceptable risks to subjects.

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

1. The sponsor decides to terminate the study based upon DSMB recommendation or its own assessment of safety
2. The sponsor decides to terminate the study at any time for administrative reasons.

8.7 Investigational Product(s)

The IP, BAX 802, is a recombinant purified form of rpFVIII from which the B domain has been deleted and replaced with a 24 amino acid linker. Recombinant pFVIII (BAX802) is expressed as a glycoprotein by a genetically engineered BHK cell line. The molecular weight of rpFVIII is approximately 175 kDa (based on its 1448 amino acid sequence) and has 86% pair-wise sequence homology with hFVIII.

BAX 802 will be supplied as white lyophilized powder in 3 mL glass vials containing nominally 500 units per vial for reconstitution with 1.0 mL sterile water for injection.

8.7.1 Packaging, Labeling, and Storage

BAX 802 will be supplied in a lyophilized form. For specific instructions for reconstitution, please refer to the Pharmacy Manual. A sufficient quantity of BAX 802 will be supplied to each study site, as well as an acknowledgement of receipt form.

The core label texts for all packaging units will be translated or adjusted, to be in compliance with applicable regulatory requirements, national laws in force and in accordance with the local languages. Minimally each vial will bear a label with the following information:

- Sponsor name
- Study number

- Pharmaceutical dosage form
- Route of administration
- Name of IP and actual quantity of dose units
- Batch number
- Space on which to record the subject number
- The statement ‘For clinical trial use only’ or ‘Caution: new drug limited by Federal Law to investigational use’ or ‘To be used only by a qualified Investigator’, as appropriate
- Name, address and telephone number of the Sponsor, Contract Research Organization or Investigator, if appropriate
- Storage conditions
- Expiry or manufacturing date, as appropriate

The Investigator or designee will only dispense BAX 802 to subjects included in this study.

BAX 802 should be kept refrigerated at 2°C to 8°C (36°F to 46°F). The following precautions should be taken:

- Do not freeze
- Do not use if frozen, even if it has been thawed
- Do not use beyond the expiration date printed on the carton or vial
- Do not use after > 3 hours of reconstitution.

8.7.2 Reconstitution and Administration

The reconstitution procedures for BAX 802 are detailed in the Pharmacy Manual. Reconstituted BAX 802 should be kept and administered at room temperature and must be administered within 3 hours of reconstitution.

BAX 802 will be administered as an intravenous bolus infusion to the cubital vein per the dosing schema for major and minor surgeries (Table 5).

8.7.3 Description of Treatment

8.7.3.1 FVIII Maintenance Plan

Based on the category (minor or major) and type of surgery and prior to intervention, the Investigator should outline the expected FVIII maintenance plan with target peak and trough levels covering the surgical, dental or invasive procedure until expected wound healing. The FVIII maintenance plan should be communicated to the medical director/designee to ensure that the recommendations regarding FVIII target levels as provided in the protocol are followed (see Table 5). Each FVIII maintenance plan for major surgeries requires prior approval of the medical director. The FVIII levels measured intra/postoperatively will be compared with the FVIII maintenance plan. Slight deviations from the predefined plan are allowed based on Investigators clinical judgment and/or available laboratory FVIII data.

It is recommended that the turnaround time for FVIII activity results from the local laboratories are ≤ 2 hours so that dosing decisions could be made and subjects are dosed adequately.

8.7.3.2 Perioperative Dosing

Adjustments to the dose and frequency of BAX 802 dosing during the intra- and postoperative period should follow the maintenance plan provided by the Investigator prior to surgery. Adjustments must be based on regular FVIII activity measurements determined at pre- and post-dosing of BAX 802 and will depend on the type of the surgery performed and the intensity of the hemostatic challenge.

8.7.3.3 Dosing Schedule and Requirements

8.7.3.3.1 General

As described in Section 8.2.2, the loading dose will be calculated according to the following formula:

Loading dose of BAX 802 (administered approximately 1 to 2 hours prior to the surgery)**:**

- **Major Surgery:**
  [80 × body weight (kg)] + [body weight (kg) × 40(1-[HCT%/100]) x anti-pFVIII inhibitor titer (BU)]
- **Minor Surgery:**
  [50 × body weight (kg)] + body weight (kg) × 40(1-[HCT%/100]) × anti-pFVIII inhibitor titer (BU)]

For example, for a 70 kg subject undergoing major surgery and having HCT 45% and anti-pFVIII inhibitor titer 3 BU, the loading dose of BAX 802 will be calculated as follows:

$$80\ (70) + 70 \times 40(1\text{-}[45/100]) \times 3 = 10{,}220\ \text{U}$$

Subsequent doses, dosing frequency, and duration of treatment will be based on clinical judgment and measured FVIII levels, and will require empirically based adjustments until hemostasis is achieved based on the following calculation below (Table 5):

- **Required (subsequent) dose (U) =** [body weight (kg) × desired FVIII rise (U/dL or % of normal)]/1.2 (U/kg per U/dL).

Table 5: Dosing for Perioperative Management

Type of Surgery	Recommended FVIII Level (% of normal or U/dL)	loading dose	Subsequent Dose
Major (see Section 8.2.1.1)	**Prior to surgery:** ≥ 80% **Postoperative up to 72 hours (if not yet discharged):** ≥ 80% **Postoperative Day 4 – Day 7 (if not yet discharged):** ≥ 50% (if not yet discharged) **Postoperative Day 8 to discharge (if not yet discharged):** it is recommended that the FVIII levels do not fall below 30% (left to the discretion of the Investigator depending on the postoperative course)	[80 × body weight (kg)] + [body weight (kg) × 40(1-[HCT%/100]) × anti-pFVIII inhibitor titer (BU)[a]], administered approximately 1 to 2 hours prior to the surgery	Titrate subsequent doses to maintain recommended FVIII trough levels and individual clinical response using following formula: Required dose (U) = [body weight (kg) × desired FVIII rise (U/dL or % of normal)]/1.2 (U/kg per U/dL)
Minor (see Section 8.2.1.2)	**Prior to surgery:** ≥ 50% **Postoperative up to 72 hours (if not yet discharged):** ≥ 50% **Postoperative Day 4 to discharge (if not yet discharged):** it is recommended that the FVIII levels do not fall below 30% (left to the discretion of the Investigator depending on the postoperative course)	[50 × body weight (kg)] + [body weight (kg) × 40(1-[HCT%/100]) × anti-pFVIII inhibitor titer (BU)[a]], administered approximately 1 to 2 hours prior to the surgery	

[a] Anti-pFVIII inhibitor titer and hematocrit information available from screening laboratory result will be used.

Note: It is recommended that the plasma levels of FVIII do not exceed 200% of normal.

If at any time during the study, a subject does not respond to BAX 802 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. In the event of unexplained, excessive bleeding, the subject will be treated by whatever means necessary until adequate hemostasis is achieved. If other rescue medications become necessary, the subject will subsequently be withdrawn from this BAX 802 surgery study and considered a treatment failure and assigned a GHEA score of 0 for remaining assessments (if any). Adverse events and the details of concomitant medication and blood product use coincident with the treatment of all unanticipated bleeding will be recorded. The use of adjunct antifibrinolytic therapy (such as tranexamic acid) is allowed if clinically indicated by the Investigator and/or according to the standard of care (SOC) of the subject's institution.

8.7.3.3.2 Preoperative and loading dose

The subject will receive a loading dose calculated according to the formula described in Section 8.7.3.3.1 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 to 120 minutes prior to surgery (prior to incision/intubation).

The recommended FVIII target level is ≥ 80% for major surgeries/procedures and ≥ 50% for minor surgeries/procedures.

It is recommended that the surgery starts after FVIII levels have achieved target levels. However, if FVIII activity post loading dose is close to the target level, a supplemental dose of BAX 802 should be administered without further delaying the surgery, based on Investigator's judgement. Close to the target for major and minor surgeries will be defined as levels of ≥ 70% for major and ≥ 40% for minor surgeries, respectively. This is 10% from the target, which is considered a normal assay variation.

If FVIII activity post loading dose is not close to the target level, a supplement dose of BAX 802 should be administered and surgery delayed until FVIII levels have achieved target levels or are in close range.

Subjects will receive subsequent doses of BAX 802 in order to achieve the FVIII target levels (see Table 5). All subsequent dosing of BAX 802 should be preceded by measurement of residual FVIII levels and dose adjustments must be based on the most recent residual FVIII activity levels.

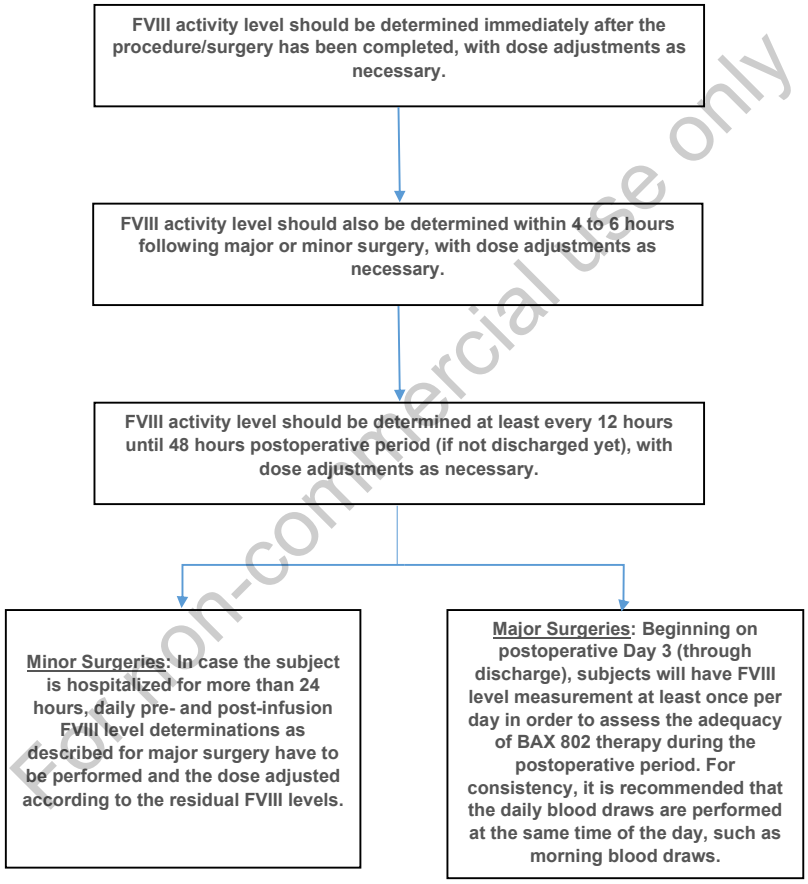
Note: It is recommended that the plasma levels of FVIII do not exceed 200%.

Note: Dose adjustments should not be based on activated partial thromboplastin time (aPTT) values.

8.7.3.3.3 Postoperative Dosing

All surgeries/procedures are to have FVIII levels monitored per the diagram in Figure 1:

Figure 1: Postoperative FVIII Monitoring



More frequent monitoring of FVIII activity is advised in subjects who have baseline anti-pFVIII inhibitor titers of ≥ 0.6 BU.

All subsequent dosing of BAX 802 must be preceded by measurement of residual FVIII levels pre-dose and FVIII level measurement 30 ±5 minutes post-dosing.

After the initial loading dose, optional re-dosings 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.

It is recommended that the FVIII trough levels are within the range targeted for major surgery during the treatment period as per Table 5. Dosing adjustments based on aPTT values are not allowed.

Any modifications of the FVIII maintenance plan that are deemed necessary during the postoperative period will be at the discretion of the Investigator and will be documented on the CRFs.

At a minimum, a blood sample for FVIII determination must be drawn prior to any supplemental unscheduled FVIII infusion and 30 ±5 minutes post-dosing.

8.7.3.3.4 Dosing for Unrelated/Surgical Site Bleeding Episodes during the Postoperative Period

Unrelated bleeding episodes and surgical site bleeding episodes are defined in Section 11.2.3.

The BAX 802 dosing regimen for treatment of these bleeding episodes will be based on the guidelines in Table 6. These guidelines may be adjusted by the Investigator based upon his or her clinical judgment.

Table 6: BAX 802 Treatment Guidelines for Unrelated/Surgical Site Bleeding Episodes

Type of Bleeding Episode	Recommended FVIII Level (%)	BAX 802 Dose
Minor Early hemarthrosis, mild muscle bleeding, or mild oral bleeding, including, epistaxis	20% to 40%	Required dose (U) = [body weight (kg) × desired FVIII rise[a] (U/dL or % of normal)]/ 1.2 (U/kg per U/dL) Titrate subsequent doses to maintain recommended FVIII trough levels and individual clinical response until the bleeding resolves.
Moderate Moderate bleeding into muscles, bleeding into the oral cavity, definite hemarthrosis, and known trauma	30% to 60%	
Major Significant gastrointestinal bleeding, intracranial, intra-abdominal, or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces or iliopsoas sheath, fractures, head trauma	60% to 100%	

[a] If the most recent residual FVIII activity level is from the measurement performed ≤ 4 hours of the bleeding episode, use this value to calculate desired FVIII rise. If the most recent residual FVIII activity level is from the measurement performed > 4 hours of the bleeding episode, the desired FVIII rise should be equivalent to the recommended FVIII level for that type of bleeding episode (as described in the column to the left).

Note: It is recommended that the plasma levels of FVIII do not exceed 200% of normal.

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

Repeat infusions of BAX 802 can be administered to treat these bleeding episodes, as per Investigator's discretion.

When bleeding is controlled, additional infusions of BAX 802 to maintain hemostasis are permitted, if required. Infusions given to treat and control the unrelated bleeding episode should be documented in the CRF.

If a subject is discharged or cannot be continued on IP at the study site, (e.g., because the clinic is closed on weekends), study participation should end at the time of hospital discharge and follow-up treatment, if any, should proceed with SOC products as per Investigator's discretion.

Note: IP (BAX 802) will not be dispensed to the subjects for in-home use.

For a detailed description of bleeding episodes into different sites see Supplement 20.6.

8.7.4 Thrombosis Prophylaxis and Topical Hemostatics

Commercially available gelatin sponges, topical thrombin, fibrin sealants, absorbable collagen preparations or anti-fibrinolytics (e.g., tranexamic acid, ε-amino caproic acid) may be used according to each institution's SOC. Details, including the dose, of all adjunctive hemostatic medication used will be recorded in the CRFs designed for this study and the reason for use given.

Thrombosis prophylaxis can be administered at the discretion of the Investigator according to the SOC of each institution and recorded into the respective CRF. Thrombosis prophylaxis should preferably consist of mechanical measures such as intermittent pneumatic compression (IPC), compression stockings and early mobilization. Pharmacologic thrombosis prophylaxis such as low molecular weight heparin (LMWH) may be considered for certain surgical interventions such as major orthopedic surgery after careful evaluation by the Investigator of the potential risks and benefits.

8.7.5 Investigational Product Accountability

The Investigator will ensure that the IP(s) 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(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. The IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center, as applicable per study design). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) 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(s) 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, 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.

No data will be entered directly onto the case report form (CRF).

For additional information on study documentation and CRFs, see Section 17.2.

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 requires a major or minor elective surgical, dental or other invasive procedure
2. Subject is male and ≥ 12 to ≤ 75 years old at the time of screening
3. Subject has provided signed informed consent (and assent for adolescent subjects, as applicable) in accordance with local regulatory requirements
4. Subject has severe (FVIII level < 1%) or moderately severe (FVIII level ≤ 2%) CHA with inhibitors to hFVIII of ≥ 0.6 BU, as tested at screening at the central laboratory
5. Subject is not currently receiving or has recently received (< 30 days) ITI therapy
6. Subject has a Karnofsky performance score of ≥ 60 at screening
7. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm3 at screening
8. Subject is hepatitis C virus negative (HCV-) by antibody or polymerase chain reaction (PCR) testing; or HCV+ with chronic stable hepatitis disease. (If positive, the antibody titer will be confirmed by PCR.)
9. Subject is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

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

1. The subject requires emergency surgery
2. Severe chronic liver dysfunction or disease (e.g., ≥ 5 × upper limit of normal [ULN] alanine aminotransferase [ALT], as confirmed by central laboratory at screening or a documented prothrombin time/international normalized ratio [PT/INR] > 1.5)
3. Clinically symptomatic renal disease (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening
4. Anti-pFVIII inhibitor > 10 BU prior to surgery
5. Platelet count < 100,000/µL at screening
6. Subject has another active coagulation disorder, other than hemophilia A, as per the medical history

7. Planned use of α-interferon with or without ribavarin for HCV infected patients or planned use of a protease inhibitor for HIV infected patients. Patients currently taking any of these medications for ≥ 30 days are eligible
8. Known hypersensitivity to rpFVIII, or hamster or murine proteins
9. Subject has an ongoing or recent (within 3 months of screening) thrombo-embolic disease, fibrinolysis or disseminated intravascular coagulation (DIC)
10. Subject has been exposed to an IP 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
11. Subject is unable to tolerate quantity of blood to be drawn for protocol procedures
12. Subject is a family member or employee of the Investigator.

9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) are described in Section 10.7, Section 20.3, and Section 20.4.

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

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

- AEs/SAEs that in the Investigator's or sponsor's opinion, poses an unacceptable risk for continued dosing in the subject
- Participation in another clinical study involving an IP during the course of the study
- The subject experiences a severe anaphylactic reaction
- The subject had uncontrolled hemorrhage that was the result of inadequate therapeutic response despite proper dosing of BAX 802, necessitating rescue therapy with bypassing agents.

10. STUDY PROCEDURES

10.1 Informed Consent

Any patient who provides informed consent or assent, as applicable (i.e., signs and dates the informed consent form (ICF) and assent form, if applicable) is considered a subject in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (241502) to be provided by the sponsor, 3-digit number study site number (e.g., 002) to be provided by the sponsor, and 3-digit subject number (e.g., 003) reflecting the order of providing informed consent. For example, the third subject who signed an ICF at study site 002 will be identified as Subject 241502-002003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure.

All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

Subjects who fail screening due to a single laboratory test result that does not meet eligibility criteria may have that laboratory test repeated at the discretion of the Investigator. This will include a repeat of only the failed assessment; complete re-screening will not be necessary. In these cases, a new SIC is not required; the subject will maintain their original SIC. The repeat of a screening assessment is allowed once. A repeat assessment must take place within 42 days of the initial screening for any subject requiring repeat of a screening assessment. If this timeframe is exceeded, then all screening assessments must be repeated and the subject assigned a new SIC. Exemptions are possible for administrative reasons and have to be approved by the sponsor. Subjects with an inadequate interval between screening and prior IP drug (other than BAX 802) administration or prior participation in a drug or device study (i.e., 30 days), may be re-screened only once and only when the required interval is reached.

The screening assessment should be performed within 45 days prior to the planned elective surgery.

The overall study design is illustrated in Supplement Figure 2. Details on the procedures to be performed at each study visit, including screening, can be found in Supplement 20.3 and Supplement 20.4.

10.4 Study Periods

The study will be divided into 5 periods:

1. Screening
2. Preoperative
3. Intraoperative
4. Postoperative
5. End of study

A detailed description of study procedures per study period is provided in Supplement 20.1.

10.4.1 Discharge/End of Study Visit

Discharge Visit will be performed when the subject is discharged. The End of Study Visit will be performed 42 ± 7 days following the completion of the surgical procedure. In cases where the Discharge Visit would occur within 3 days of the End of Study Visit, the respective visits can be done as a single visit. Sites must make every effort to complete 3 independent GHEA assessments (GHEA1, GHEA2, GHEA3) for both minor and major procedures, preferably allowing for as much time as possible to pass between assessments within the windows specified in this protocol.

10.4.2 Antibody Testing Visit

A visit will be performed between 7 to 14 days after last perioperative dose of BAX 802. Study procedures will be performed as per Table 9 and blood samples will be collected for antibody testing and other tests as per Table 10.

10.4.3 Unscheduled Visit

An unscheduled visit could be performed for events such as antibody testing or management of bleeding episodes.

10.5 Medications and Non-Drug Therapies

The following medications are **not** permitted before discharge (unless used as rescue medications or used to treat unrelated/surgical site bleeding episodes as specified below):

Medications:

- Hemophilia inhibitor bypassing therapy (recombinant factor VIIa [NovoSeven] within 3 hours or activated prothrombin complex concentrate [aPCC; FEIBA]) within 12 hours prior to initial BAX 802 administration) unless used as a rescue medication (Section 10.5) after failure/study withdrawal or used to treat unrelated/surgical site bleeding episodes (Section 11.2.3).
- Hemophilia medication other than BAX 802 at any time during the study.

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

The following medications and non-drug therapies are permitted within 30 days before study entry and during the course of the study:

Medications:

- The management of a serious thrombo-embolic event may require anticoagulant medication and this may need to be administered concurrent with the use of BAX 802 to ensure that a re-bleed or continuing severe hemorrhage does not occur on withdrawal of BAX 802 (see Section 10.6). In such instances the Sponsor's medical monitor should be consulted.
- Any medications deemed necessary by the subject's physician to treat or prevent any medical condition (with the exception of those listed as not permitted)
- Any over-the-counter medication used by the subject to treat symptoms or signs of any medical condition
- Supplemental vitamins and minerals

Non-drug therapies:

- Any non-drug therapy (e.g., physiotherapy) deemed necessary by the subject's physician to treat or prevent any medical condition

10.6 Rescue Medications

Bypassing agents (FEIBA or NovoSeven) can be used as a rescue medication if expected plasma FVIII activity levels are not attained or if bleeding is not controlled despite proper dosing of BAX 802 during the intra- or postoperative period of the study.

Note: At least 2 doses of BAX 802 need to be administered before the subject is considered to be a treatment failure and switched to the rescue medication.

10.7 Subject Completion/Discontinuation

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

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], and dropout), physician decision (e.g., progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the Investigator, e.g., technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate 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 20.3 and Supplement 20.4.

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.

10.8 Procedures for Monitoring Subject Compliance

Subject compliance with the procedures and treatment(s) outlined above will be monitored by direct review of the subject's source data at the sites and evaluated against the protocol requirements. Additionally, electronic edit checks will be performed on all protocol-specified procedures and treatment data that are collected to ensure quality and accuracy. Deviations from the protocol-specified procedures and treatments will be noted in the final study report.

All study procedures are to be performed under the direct supervision of the Investigator/a licensed healthcare professional at the study site, and thus, no separate procedures will be used to monitor subject compliance.

11. ASSESSMENT OF EFFICACY

11.1 Primary Efficacy Endpoint: Global Hemostatic Efficacy Assessment Score

The primary outcome measure is the proportion of all surgical or other invasive procedures with a "good" or "excellent" response measured by GHEA. The GHEA score is composed of 3 individual categorical ratings (GHEA1, GHEA2, GHEA3) which will be added together to form the total GHEA score according to Table 1 (see Section 8.4.1).

11.2 Secondary Efficacy Endpoints

11.2.1 Blood Loss

The observed versus predicted (recorded prior to surgery) operative blood loss will be described for the period from initiation of the intervention to discharge or 24 to 72 hours after the last perioperative treatment dose of BAX 802 (whichever is first), as applicable.

Prior to the surgery, the surgeon/Investigator will predict the estimated volume (in 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 and from completion of the procedure until approximately 24 hours post-surgery and for the overall perioperative time period (assessed at discharge or 24 to 72 hours after the last perioperative treatment dose of BAX 802). The expected normal/average, and maximal blood loss and transfusion requirement estimate will be timestamped into the source documentation and/or blood loss form prior to the surgery, and then transferred into the CRF. No changes will be allowed to these estimates after the surgery.

The intraoperative blood loss will be measured by determining the volume of blood and fluid removal through suction into the collection container (waste box and/or cell saver) and the estimated blood loss into swabs and towels during the procedure, per the anesthesiologist's record.

Postoperatively, blood loss will be determined by the drainage volume collected, which will mainly consist of drainage fluid via vacuum or gravity drain, as applicable. In cases where no drain is present, blood loss will be determined by the surgeon's clinical judgment, as applicable or entered as "not available".

11.2.2 Blood Transfusions

The type and volume (in mL) of blood products will be recorded from initiation of the intervention to discharge or 24 to 72 hours after last perioperative treatment dose of BAX 802 (whichever is earlier). Furthermore, also salvage of blood obtained from autologous transfusion systems, (e.g., cell savers) will be recorded. In addition, the type and volume of fluid replacement and volume expanders will be recorded as concomitant medication (e.g., volume of salvaged blood, red blood cells, platelets and other blood products transfused).

11.2.3 Bleeding Episodes

[redacted], until the time of discharge or until the subject resumes his previous treatment regimen, whichever is later.

Any subject who is deemed to have excessive, unexplained bleeding will have blood drawn for measurement of FVIII levels.

Bleeding episodes will be classified as follows:

- Unrelated bleeding episodes: an unrelated bleeding episode is defined as any bleeding occurring at a different anatomical site than the surgery site during the postoperative period.
- Surgical site bleeding episodes: Surgical site bleeding episodes are any bleeding at the surgical/procedure site which occurs after discharge (related to the perioperative procedure) or 72 hours after the last perioperative treatment dose of BAX 802 (if hospitalization is prolonged for reasons other than perioperative procedures), whichever is earlier.

These bleeding episodes will be treated as follows:

- If these unrelated bleeding episodes or surgical site bleeding episodes occur during the subject's stay in hospital, it is recommended that subjects are treated with BAX 802. BAX 802 will be dosed as per the most recent residual FVIII activity level and clinical judgment using the dosing regimen provided in Table 6 [Required dose = body weight (kg) × desired FVIII rise (U/dL or % of normal)]/ 1.2 (U/kg per U/dL)]. All subsequent dosing of BAX 802 should be preceded by measurement of residual FVIII levels and dose adjustments must be based on the most recent residual FVIII activity levels.

- If these unrelated bleeding episodes or surgical site bleeding episodes occur after the subject has been discharged, subjects may be treated with BAX 802 or SOC, as per Investigator's discretion. Note: IP (BAX 802) will not be dispensed to the subjects for in-home use.

An unscheduled visit could be performed for the management of bleeding episodes.

11.2.4 BAX 802 Administration

The daily and total weight-adjusted administration of BAX 802 per subject will be recorded.

11.2.5 Hemostatic Efficacy Rating for Treatment of Unrelated/Surgical Site Bleeding Episodes

An unrelated bleeding episode is defined as any bleeding occurring at a different anatomical site than the surgery site during the postoperative period. Surgical site bleeding episodes are any bleeding at the surgical/procedure site which occurs after discharge (related to the perioperative procedure) or 72 hours after the last perioperative treatment dose of BAX 802 (if hospitalization is prolonged for reasons other than perioperative procedures), whichever is earlier. These bleeding episodes will be treated as per Section 11.2.3.

If subject is treated with BAX 802 for unrelated bleeding episodes or surgical site bleeding episodes, the subject will rate the severity (minor, moderate, or major) of the bleeding episode and will rate the overall treatment response at 24 ±2 hours after the initiation of treatment and at the resolution of bleed (if not resolved within 24 hours) using a 4-point efficacy rating scale (Table 7). Since the efficacy rating is based to a large degree on cessation of pain, the Investigator/subject shall, particularly in the event of injury-related bleeding into ≥ 1 location, consider the injury-related symptoms when performing the efficacy rating 24 hours after initiating treatment and at resolution of bleed. Data should be collected as an unscheduled visit.

As per Table 5, multiple infusions of BAX 802 may be administered for the treatment of a bleeding episode. The overall response to all infusions combined is the rating that will be recorded at resolution of bleed.

Table 7: Efficacy Rating Scale for Treatment of Unrelated/Surgical Site Bleeding Episodes

Excellent	Full relief of pain and/or cessation of objective signs of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution.
None	No improvement or condition worsens.

As per Table 5, multiple infusions of BAX 802 may be administered for the treatment of a bleeding episode. The overall response to all infusions combined is the rating that will be recorded at resolution of bleed.

11.3 Factor VIII Activity

Blood will be obtained for assessment of FVIII activity at screening (tests to be performed at the **central laboratory**). Results from **local laboratory** will be used to make any dosing decisions.

Blood will be obtained for assessment of FVIII activity for patient management purposes at the following time points (tests to be performed at the **local laboratory**, with additional back-up samples to be tested in 1 batch at the **central laboratory**):

- Within 30 minutes prior to the administration of the initial loading dose preoperatively and 30 ±5 minutes post-infusion. If re-dosing with BAX 802 is required to obtain the required FVIII levels, an additional blood sample needs to be drawn 30 ±5 minutes following the re-dosing with BAX 802.
- Postoperatively until day of discharge from the investigative site: daily within 30 minutes prior to the infusion of BAX 802 and 30 ±5 minutes post-infusion. Pre- and post-dosing blood draws for FVIII activity level determination should also be performed for each BAX 802 administration.
- FVIII activity will also be assessed if the subject has excessive, unexplained bleeding at any time intra-or postoperatively, or whenever deemed necessary according to the institution's SOC.

11.3.1 Blood Sampling and Processing for FVIII Analysis

At each blood sampling time point whole blood will be collected in blood sampling tubes will be collected in S-Monovette® tubes (Sarstedt, Nümbrecht, Germany) containing 3.2% trisodium citrate, or equivalent blood drawing equipment (e.g., Vacutainer tubes), and immediately mixed. The citrated whole blood samples will be capped and transported at room temperature (i.e., 20 to 25°C) to the local clinical laboratory for centrifugation, processing, and storage. Monovettes must be kept in an upright position at all times to avoid leakage.

All samples taken through 6 hours post-dosing will be collected from an extremity other than that used for the infusion of study product. Thereafter, either extremity may be used to obtain samples.

If the subject has a central 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 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 sample.

All citrated plasma samples will be stored and shipped to the central laboratory at ≤ -70°C for testing.

All back-up samples collected during the perioperative period will be shipped to the central laboratory as soon as possible in 1 batch and analyzed, as needed.

Blood samples will be analyzed for FVIII activity (1-stage clotting assay and the chromogenic assay) at the central laboratory. The 1-stage FVIII activity assay will serve as the primary assay; the chromogenic assay of FVIII activity will be used to provide supportive data. Local laboratories are expected to use a 1-stage clotting assay.

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 (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that at any dose meets 1 or more of the following criteria:

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

- Thrombo-embolic events (e.g., stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism).
- The confirmed development of de-novo anti-pFVIII inhibitory antibodies or increases of > 10 BU in pre-existing titers of anti-pFVIII inhibitory antibodies (see Section 12.1.1.1.1)

Planned hospitalization for any study procedures as per the protocol will not be considered as an SAE.

12.1.1.1.1 Inhibitory Serious Adverse Events

The development of de-novo anti-pFVIII inhibitory antibodies (≥ 0.6 BU) must be confirmed with a second blood draw 7 to 14 days after the initial confirmed positive de novo result (or repeat testing of original sample if a second draw is not possible). Confirmation of de novo inhibitory antibodies or a confirmed increase of > 10 BU in pre-existing titers of anti-pFVIII inhibitory antibodies must be reported as a SAE within 24 hours, and followed up.

Increases in pre-existing titers of anti-pFVIII inhibitory antibodies will require a second confirmatory test 7 to 14 days after the initial confirmed positive increase (or repeat testing of original sample if a second draw is not possible). If the protocol-defined significant increase (> 10 BU) is confirmed, it will be reported as an SAE.

Safety will be further monitored by the Investigator and medical monitor to evaluate the clinical significance of the inhibitor level. Although the development of, or increase in, anti-pFVIII inhibitory antibody titers may not necessarily indicate a failure of response to BAX 802, the inhibitor levels and patient response will be closely monitored and an alternative therapy will be considered for lack of efficacy, if applicable.

12.1.1.2 Suspected Unexpected Serious Adverse Reaction

Any suspected adverse reaction to study treatment that is both serious and unexpected.

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

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

Once determined to meet the criteria for a SUSAR, an SAE should be submitted to regulatory agencies expeditiously.

12.1.1.3 Non-Serious Adverse Event

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

12.1.1.4 Unexpected Adverse Events

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). "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 product, but are not specifically mentioned as occurring with the particular product under investigation. The expectedness of AEs will be determined by the sponsor using the Company Core Data Sheet for OBIZUR as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.

12.1.1.5 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 are collected under other study endpoints and thus are not reportable on the AE CRF, nor will they be included in the analysis of AEs:

Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be assessed as part of the efficacy assessments. However, the Investigator may decide that the event is an AE if the event also would have occurred in a normal patient under the same circumstances. If a bleeding episode was caused by an injury, the injury will be reported as an AE. All bleeding episodes must be entered in the bleeding event CRF.

All other/Each AE from the first IP exposure until study completion or 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 (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, or unknown) and if applicable action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

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

If an Investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the provided SAE Report 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, for example, assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the Investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs

- Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).

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

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

12.1.2.3 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Table 9) and Section 12.1.

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

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the IP, must be reported immediately (within 24 hours of the study center's first knowledge of the event).

Any SAEs must be reported using the paper SAE Report Form to meet the 24 hour timeline requirement (for contacts and instructions refer to the SAE Report Form).

The initial SAE information reported on the applicable SAE Report Form must at least include the following:

- Protocol number
- Subject identification number and demographics (gender, age at onset of event and/or date of birth)
- IP exposure
- Medical Term for Event (Diagnosis preferably)
- Description of the (S)AE, including:
  - Date of onset
  - (S)AE treatment (drug, dose, route of administration)
  - Causal relationship by the Investigator
  - Measures taken (i.e., action taken regarding IP in direct relationship to the AE)
- Seriousness criteria (i.e., death, life-threatening, or other criterion)
- Cause of death
- Autopsy findings (if available)
- Name, address, fax number, email, and telephone number of the reporting
- Investigator

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 (ECs) and relevant competent authority(s) are notified of the urgent safety measures 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 (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the AE CRF (and SAE Report Form if CRF is not available). These events will not be considered as SAEs and will not be included in the analysis of SAEs.

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

- Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be assessed as part of the efficacy assessments. If a bleeding episode was caused by an injury, the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (e.g., abrasion of skin). Therefore, any hemophilia-related event (e.g., hemarthrosis [presenting as swelling, pain, and decreased range of motion], bruising, hemorrhages, or pain at bleeding episode site) will not be reported as AEs. However, the Investigator may decide that the event is an AE if the event also would have occurred in a normal patient under the same circumstances.

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.** The NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g., reconstitution difficulty
- Missing components

- Damage to the product or unit carton
- A mislabeled product (e.g., 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.

Medical history will include the collection of hemophilia history, bleeding episode history, and history of aPCC or rFVIIA usage for 6 months prior to screening. Relevant medical and surgical history and all medications taken 3 months prior to screening will also be collected.

All medications taken and non-drug therapies received within 3 months before providing informed consent until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Table 9), 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 12.1.1.5), 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

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

The hematology panel will consist of complete blood count (hemoglobin, HCT, erythrocytes [i.e., red blood cell count), and leukocytes (i.e., white blood cell count]) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, and neutrophils) and platelet counts.

Clinical chemistry and hematology assessments will be performed on EDTA-anticoagulated serum and whole blood, respectively, at the central laboratory. The frequency of blood draws for clinical and hematology assessments is provided in Table 10.

Details of blood sampling volumes are presented in the laboratory manual and master ICF.

12.7.1 Hematology, Clinical Chemistry, and Urinalysis

The hematology panel will consist of complete blood count (hemoglobin, HCT, erythrocytes [i.e., red blood cell count], and leukocytes [i.e., white blood cell count]) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

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

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening/baseline, all study visits (i.e., pre- and perioperatively and daily while the patient is at the study site), and at study completion/termination. Hematology and clinical chemistry assessments will be performed on EDTA-anticoagulated whole blood and serum, respectively, at the central or local laboratory.

The urinalysis panel will consist of pH, protein, ketones, glucose, bilirubin, blood, urobilinogen, specific gravity by dipstick and microscopy if any findings are abnormal.

Urine will be obtained for assessment of urinalysis parameters at screening and at the postoperative hemostatic efficacy assessment, antibody testing visit, and End of Study visit.

12.7.2 Viral Serology

Viral serology testing will include HIV-1 and HIV-2 antibody, HAV (immunoglobulin M [IgM] and total antibodies), hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), HCV antibody, and parvovirus B19 (IgM and immunoglobulin G [IgG] antibodies). The HIV and HCV titer will be confirmed by PCR for all subjects reported as HIV and HCV positive. All viral serology assessments will be performed at screening. Any positive HBsAg test will be repeated using a new blood sample.

12.7.3 Immunogenicity

Immunogenicity assessments will include anti-pFVIII and hFVIII binding (IgG and IgM) and inhibitory antibodies and anti-BHK binding antibodies.

Blood samples will be collected for the assay of anti-pFVIII and hFVIII binding and inhibitory antibodies and anti-BHK binding antibodies at the times indicated in Table 9 and Table 10.

All FVIII assays related to study subject management decisions by the Investigator will be performed at the Investigator's local laboratory.

A central reference laboratory will perform assays (anti-pFVIII, anti-hFVIII, and anti-BHK) on samples taken at the times indicated in Table 9 and Table 10.

Binding antibodies to human and porcine FVIII (both IgG and IgM) and binding antibodies to BHK proteins will be analyzed using validated enzyme-linked immunosorbent assays (ELISAs) using a multi-tiered approach consisting of screening assay, titer determination and confirmation of specificity. [redacted]

The assessment of inhibitory antibodies to pFVIII and hFVIII will be determined using a Bethesda assay (with the Nijmegen modification if possible). Further details on blood collection, tube preparation and shipment will be provided in the Laboratory Manual.

12.7.4 Assessment of Laboratory Values

12.7.4.1 Assessment of Abnormal Laboratory Values

The Investigator's assessment of each laboratory value will be recorded on the CRF. For each abnormal laboratory value, the Investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the Investigator will indicate if the value constitutes a new AE (see definition in Section 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 12.1.1.5), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the Investigator will indicate the reason, i.e., because it is due to a preexisting disease, due to a laboratory 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.

12.7.5 Backup Samples and Biobanking

Backup samples taken and stored short-term may be used for re-testing, follow-up of an AE(s) or other test results (such as FVIII activity and antibody testing), and/or assay development.

After study testing is completed, the remaining samples may be stored in a coded form for no more than 2 years after final study report completion and then the samples will subsequently be destroyed.

For this study, no samples will be taken or stored long-term in a biobank for future analyses.

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) measured once at screening, and weight (lb or kg) will also be collected.

Vital signs will be measured at screening and within 30 minutes before and 30 ±5 minutes after administration of IP, at each study visit, at any unscheduled assessments, and at study completion/termination. 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.

12.9 Karnofsky Performance Test

The Karnofsky Performance Test is a status scale (0 to 100) utilized to measure the level of activity and medical care requirements in subjects. It is an Investigator based assessment of patient status which evaluates the subjects' ability to carry on normal life activities, as well as the symptoms of their disease.[19] Subjects will be scored using this scale at screening.

12.10 Special Treatment Considerations

Patients will be screened for eligibility in the study as described in the inclusion/exclusion criteria (Section 9.1 and Section 9.2), and will be informed of the study specific restrictions and requirements of the study. Patients who are not willing to comply with the study requirements and restrictions of the study will not be eligible for enrollment.

All biological agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include, but are not limited to:

- skin rash
- pruritus (itching)
- urticaria (hives)
- angioedema (e.g., swelling of the lips and/or tongue)
- anaphylactic reaction.

Proteins may also cause redness, itching, swelling, or pain locally at the infusion site.

Sometimes, these reactions can be life-threatening. Therefore, all patients should be closely monitored for signs or symptoms that could result from such reactions, educated on the signs or symptoms of these types of reactions, and instructed to contact the study site immediately if any of the symptoms are experienced following an injection.

If a patient experiences an acute allergic/hypersensitivity reaction after an injection of IP, he should be managed appropriately and given instruction to receive relevant supportive care. Additionally, for an event judged by the Investigator to be a potential systemic allergic/hypersensitivity reaction, blood samples will be collected for anti-pFVIII, anti hFVIII, and anti-BHK binding antibodies. Serious adverse events related to development or worsening of inhibitors are described in Section 12.1.1.1.1.

Patients who experience a potentially severe allergic reaction will be discontinued from study drug, they will complete an End of Study Visit, and will be monitored for stabilization, or resolution of the AE. Premedication to prevent allergic reactions will not be permitted as severe allergic reactions are an outcome measure for this study.

13. STATISTICS

All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the statistical analysis plan (SAP).

13.1 Sample Size and Power Calculations

The total sample size for the study is 12 evaluable subjects, which includes at least 12 surgeries/procedures in 12 evaluable male subjects (at least 5 major surgeries/procedures in 5 evaluable subjects) and at least 2 of the 12 subjects are adolescents (≥ 12 to < 18 years old). The sample size, as defined in the protocol, was chosen to provide sufficient evidence of safety and effectiveness for this indication and is not based on statistical considerations.

Evaluable subjects are defined as subjects who met all study entry criteria and who had at least 1 hemostatic efficacy assessment as per Section 8.4.1.

13.2 Analysis Sets

Classification into the analysis sets will be conducted prior to the database lock.

13.2.1 Safety Analysis Set

The safety analysis set (SAS) will be comprised of all subjects who received any amount of BAX 802.

13.2.2 Efficacy Datasets

13.2.2.1 Full Analysis Set

The FAS will be comprised of all surgeries with at least 1 available hemostatic assessment.

13.2.2.2 Per-Protocol Analysis Set

The per-protocol (PPAS) analysis set will be comprised of all surgeries with evaluable ratings for all 3 perioperative hemostatic efficacy assessments, whose subjects met all study entry criteria and had no major protocol violations that might impact hemostatic efficacy assessments.

13.3 Handling of Missing, Unused, and Spurious Data

A subject who withdraws prior to the last planned observation in a trial period will be included in the analyses up to the time of withdrawal.

For surgeries with ≤ 2 missing hemostatic assessments that did not necessitate rescue therapies, the rating of "fair" will be imputed for the missing assessment. These surgeries will be included in the FAS.

13.4 Methods of Analysis

For qualitative parameters, the population size (N for sample size and n for available data) and the proportion (of available data) for each class of parameters will be presented. Quantitative parameters will be summarized by the population size (N for sample size and n for available data), mean, standard deviation, median, minimum, and maximum values.

13.4.1 Primary Outcome Measure

The primary efficacy measure will be the overall assessment of hemostatic efficacy assessed intraoperatively and at postoperative Day 1 (postoperative period, i.e., from end of surgery to 24 ±6 hours post-surgery) by the surgeon and perioperatively at 24 to 72 hours after the last perioperative treatment dose of BAX 802 or discharge (whichever is earlier) by the Investigator (hemophilia physician), and where possible, by both the Investigator and the operating surgeon (assessment by both is strongly recommended), and will be the sum of intraoperative, postoperative, and perioperative GHEA scores as rated "excellent", "good", "fair" or "none". In cases where there are differing assessments, the Investigator's assessment will be used.

If discharge is delayed for a reason other than surgery related bleeding (e.g., pneumonia), an assessment at 24 to 78 hours after last perioperative treatment dose of BAX 802 will ensure that the overall perioperative assessment is completed close to the last administered study drug dose. Wherever possible (except for intraoperative assessment), bleeding should be assessed by both operating surgeon and Investigator. To achieve the hemostatic efficacy success criteria, the study needs to achieve a ≥ 70% rate of hemostatic efficacy assessments with an "excellent" or "good" outcome in at least 12 procedures.

Hemostatic efficacy success is defined as an "excellent" or "good "outcome for ≥ 70% of hemostatic efficacy assessments.

Due to the possibility of a subject undergoing multiple surgeries, the statistical analysis of the primary outcome measure will be reported on the by-surgery level (i.e., not by the number of subjects). In cases where two or more surgical procedures are performed in the same intraoperative settings (under the same anesthesia, e.g., bilateral knee replacement) the surgery will be counted as one surgery.

Blood loss assessment from those surgeries will be assessed as one. In the event that the subject is planning to have additional surgery in the future, they will need to complete the study and be re-screened again (if > 3 months from the screening) to ensure that they continue to meet the eligibility criteria.

Point estimates and corresponding 2-sided exact Clopper-Pearson confidence intervals (CIs) at the 95% confidence level will be calculated for the rate of hemostatic efficacy assessments with excellent/good outcome for descriptive purposes.

The proportion of all surgeries and of all major surgeries with hemostatic success will be reported along with exact 95% CIs. A treatment success will be defined as a rating of excellent or good.

The primary efficacy analysis will be based on the FAS population. As a supportive analysis, the same analyses will also be carried out on the PPAS population.

A sensitivity analysis based on the first surgery will be performed if more than 20% of subjects have multiple surgeries. Any blood loss which is considered as unrelated bleeding (defined as any bleeding occurring at a different anatomical site other than the surgery site during the postoperative period, see Section 11.2.5) will not be taken into account for while making assessment of hemostatic efficacy for the primary efficacy measure.

13.4.2 Secondary Outcome Measures

13.4.2.1 Secondary Hemostatic Efficacy Analysis

Secondary outcome measures will be reported at the surgery level rather than the subject level. Descriptive statistics will be used to summarize the actual blood loss and transfusion requirements.

The summary of average daily and total weight-adjusted doses (average through postoperative 24 to 72 hours after last perioperative treatment dose of BAX 802 or discharge [whichever is earlier]) of BAX 802 per subject as well as the occurrence of bleeding episodes will be provided using descriptive statistics.

The proportion of major surgeries with good or excellent hemostatic score together with its 2-sided 95% CI will be reported for descriptive purposes.

The secondary efficacy analysis will be performed on the FAS only.

13.4.2.2 Safety Analysis

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by presenting the number and proportion of subjects having any AE, having an AE in each system organ class, and having each individual AE as reported by preferred term. In the summaries, AEs will be counted only once per patient. If a patient reports the same AE more than once, it will be counted with its worst severity and closest relationship to the study product.

The number of subjects who experienced SAEs and the number of SAEs will be tabulated. In addition, the number of subjects who experienced AEs related to IP and the number of IP-related AEs will be tabulated and subcategorized for thrombo-embolic events, inhibitory and total binding antibodies (IgG and IgM) to pFVIII and hFVIII, and binding antibodies to BHK proteins.

A listing of all AEs will be presented by subject identifier, age, preferred term, and reported term of the AE, duration, severity, seriousness, action taken, outcome, causality assessment, onset date, stop date, and medication or non-drug therapy to treat the AE. An overview table for AEs will be provided, presenting the number of AEs, the number of subjects with AEs and the corresponding percent of subjects in total, and by seriousness and relationship to study treatment. An additional summary table will present the total number of (mild, moderate, severe) AEs by system organ class and preferred term with relationship to IP.

Summary statistics over time will be presented for the continuous laboratory parameters. Descriptive statistics of changes from baseline (prior to BAX 802 loading dose before the surgery) by study visits will also be presented.

A frequency table of results of categorical laboratory parameters will be produced. Furthermore, laboratory abnormalities will be analyzed by shift tables where each subject will be counted only once with the worst grade in the summary tables.

All laboratory data will be listed with abnormal values.

Vital signs assessments as well as the corresponding changes from baseline will be summarized descriptively at each scheduled or unscheduled assessment.

The safety analysis will be based on the SAS.

13.4.1 Exploratory Outcome Measures

[redacted]

[redacted]

[redacted]

[redacted]

Further details will be included in the SAP.

13.5 Planned Interim Analysis of the Study

No interim analyses are planned for this study.

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 Institutional Review Board (IRB) or Ethics Committee (EC), and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the Investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the CTA.

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 national and local regulatory requirements as described in the CTA. The Investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "Investigator" as used in this protocol as well as in other study documents, refers to the Investigator or authorized study personnel that the Investigator has designated to perform certain duties. Sub-Investigators or other authorized study personnel are eligible to sign for the Investigator, except where the Investigator's signature is specifically required.

15.1.1 Investigator Report and Final Clinical Study Report

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

15.2 Training

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

15.3 Monitoring

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

15.4 Safety Monitoring

The safety of the subjects in this study shall be monitored by an external DSMB comprised of experts in the field of hemophilia research and clinical care.

The DSMB will review safety data at predefined intervals and make recommendations to the study team on study conduct including dose escalation and modifications to study plan. Details of the composition and responsibilities of the DSMB will be provided in a DSMB charter.

15.5 Auditing

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

15.6 Non-Compliance with the Protocol

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

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

15.7 Laboratory and Reader Standardization

Not applicable; a central laboratory/reader will be used for all clinical assessments. Local laboratories are requested to provide their laboratory specifications for each assay used.

16. ETHICS

16.1 Subject Privacy

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

16.2 Ethics Committee and Regulatory Authorities

Before patients participate in this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information 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(s) approval, as described in the CTA.

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

16.3 Informed Consent

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

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

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

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

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, screening information, CRFs, SAERs, laboratory reports (if applicable), and data clarifications requested by the sponsor.

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

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

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

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

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 CTA.

19. PUBLICATION POLICY

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

20. SUPPLEMENTS

20.1 Procedures per Study Period

Table 8: Summary of Required Procedures for Baxalta Clinical Study 241502

1. Screening

Written Informed Consent must be obtained prior to any study-related procedures

Screening activities should be performed within 45 days prior to the planned elective surgery.

The following screening procedures are required:

- Eligibility evaluation (review of inclusion/exclusion criteria)
- Hemophilia history, bleeding episode history, history of aPCC or rFVIIA usage for a year prior to screening
- Relevant medical and surgical history and all medications taken 3 months prior to screening
- Review of concomitant medications/non-drug therapies
- Physical examination (see Section 12.6)
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measure body weight and height; see Section 12.8)
- Karnofsky performance test assessment (see Section 12.9)
- Clinical laboratory assessments (see Table 10).

Table 8: Summary of Required Procedures for Baxalta Clinical Study 241502

2. Preoperative Procedures

Subjects will return to the study site prior to their scheduled surgery as instructed by site staff. Subjects will undergo the following procedures:

Prior to surgery

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

- Accurate prediction of volume of expected blood loss intraoperatively (from completion of the procedure until approximately 24 hours post-surgery) and for the overall perioperative time period (up to 24 to 72 hours after the last perioperative treatment dose of BAX 802 or discharge), which is to be timestamped into the source documentation and/or blood loss form prior to the surgery.

Loading Dose and Post Dosing Laboratory Assessment

Within 1 to 2 hours before initiating surgery, the subject will receive a loading dose of BAX 802 to raise the plasma level of FVIII to ≥ 80% for major and to ≥ 50% for minor surgical, dental and invasive procedures.

Subjects will undergo the following procedures:

- **Prior to BAX 802 loading dose:**
  - Record AEs, concomitant medications, and non-drug therapy use
  - Physical examination, vital signs (pulse rate, respiratory rate, blood pressure, and temperature) and weight
  - Laboratory Assessments including:
    - Hematology (without differential but including platelets)
    - Clinical chemistry
    - Within 30 minutes before loading dose, blood draw for:
      - FVIII activity
- **BAX 802 loading dose:**
  - Loading dose of BAX 802 to raise the plasma level of FVIII to ≥ 80% of normal for major and to ≥ 50% for minor surgical, dental and invasive procedures. It will be administered within 1 to 2 hours prior to surgery (prior to incision/intubation).
- **After BAX 802 loading dose:**
  - Laboratory assessment of FVIII activity: 30 ±5 minutes after infusion of the loading dose
  - Vital signs (pulse, respiratory rate, blood pressure and temperature) will be recorded 30 ±5 minutes after infusion
  - Confirmation that FVIII is adequate just prior to intubation/incision. Administration of additional dose of BAX 802, if required. If another dose of BAX 802 is necessary, an additional post-infusion FVIII activity determination must be performed 30 ±5 minutes following the infusion.
  - All samples taken through 6 hours post-infusion will be collected from an extremity other than that used for the infusion of study product. Thereafter, either extremity may be used to obtain samples.

The surgery may begin only if FVIII is in target range (Table 5 and Section 8.7.3.3.2).

Throughout: Monitoring of AEs and concomitant medication and non-drug therapy use.

Table 8: Summary of Required Procedures for Baxalta Clinical Study 241502

3. Intraoperative Procedures (end of surgery = Day 0)

During the surgical procedure:

- Record AEs and concomitant medication and non-drug therapy use
- Record blood product usage, including salvaged blood, packed red blood cells (pRBC), platelets, and other blood products.
- Administer additional BAX 802 infusions according to the dosing regimen (Table 5)
- Record intraoperative blood loss and transfusion requirements

If the subject has excessive or unexplained bleeding, blood draws for FVIII activity. Treat by whatever means necessary until adequate hemostasis is achieved. If rescue medications become necessary, the subject will subsequently be withdrawn from this BAX 802 surgery study and be considered a treatment failure.

After the surgical procedure:

- Record the volume of blood loss during surgery and amount of total blood product usage, including salvaged blood, packed red blood cells (pRBCs), platelets, and other blood products
- Assess intraoperative hemostatic efficacy (Global Hemostatic Efficacy Assessment, GHEA1, Table 2) (at the end of surgery)
- Take sample for FVIII activity immediately after surgery completion, with dose adjustments as necessary on the day of surgery (see Section 10.5)
- Take sample for FVIII activity within preferably 4 to 6 hours following surgery, with dose adjustments as necessary on the day of surgery (see Section 10.5)

If the subject has excessive or unexplained bleeding, blood draws for FVIII activity. Treat by whatever means necessary until adequate hemostasis is achieved. If rescue medications become necessary (see Section 10.5), the subject will subsequently be withdrawn from this BAX 802 surgery study and considered a treatment failure.

Table 8: Summary of Required Procedures for Baxalta Clinical Study 241502

4. Postoperative Procedures (Day 1 to discharge)

- For subjects undergoing major surgery: keep pre-infusion FVIII levels at least at 80% of normal for the first postoperative 72 hours and at least at 50% during postoperative Day 4 to Day 7. It is recommended that the FVIII levels do not fall below 30% from Day 8 until discharge.
- For subjects undergoing minor surgery: keep pre-infusion FVIII levels at least at 50% of normal for the first postoperative 72 hours. It is recommended that the FVIII levels do not fall below 30% from Day 4 until discharge.

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

- Record AEs and concomitant medication and non-drug therapy use
- Record blood loss on a daily basis and at drain removal, if applicable
- Record transfusion requirements
- GHEA:
  - GHEA2 (Table 3): assessment of postoperative hemostatic efficacy of BAX 802 performed at Day 1 by the operating surgeon/Investigator
  - GHEA3 (Table 4): assessment of perioperative hemostatic efficacy of BAX 802 at 24 to 72 hours after the last perioperative treatment dose of BAX 802 or discharge (whichever is earlier) performed by the Investigator, and where possible, also by the operating surgeon

  If a subject leaves the facility on the day of the surgery/invasive procedure, it is required to have a site visit the next day (Day 1) and at 24 to 72 hours after the last perioperative treatment dose of BAX 802 to perform the assessments of postoperative (GHEA2) and perioperative (GHEA3) hemostatic efficacy, respectively.
- Perform physical examination and vital signs (pulse, respiratory rate, blood pressure and temperature) on Days 1, 2, 3, and 7 post surgery (if a subject remains admitted).
- Blood draws for FVIII activity determination and hematology should be performed coincident with an early morning dose to the greatest extent possible.
- FVIII activity assays at the local and the central laboratories as per Section 8.7.3.3.3. Additional BAX 802 doses will be administered as per Table 5. FVIII activity assays pre infusion (within 30 minutes) and post infusion (30 ±5 minutes) for each IP administration, and at other time points as deemed necessary by the surgeon or Investigator throughout the study
  - 1-stage clotting and chromogenic for the central laboratory
  - 1-stage clotting for local laboratories
- Samples for laboratory testing will be taken daily during Day 1 to 7 post-surgery and then subsequently once weekly:
  - Hematology
  - Clinical chemistry

- If the subject has excessive or unexplained bleeding, blood draws for FVIII activity. Treat by whatever means necessary until adequate hemostasis is achieved. If rescue medications become necessary, the subject will subsequently be withdrawn from this BAX 802 surgery study and considered a treatment failure.
- If the subject is discharged from surgical facility on the day of the procedure, he should attend the site on Day 1 to perform the postoperative hemostatic efficacy assessment (Day 1 assessment) and the overall perioperative assessment. In this case, physical examination, vital signs, laboratory assessments, adverse events, and concomitant medications must also be assessed. If the subject is discharged from surgical facility after Day 1 but prior to the overall perioperative assessment, he should return to the site for that assessment as well as the required physical examination, vital signs, laboratory assessments, adverse events, and concomitant medications assessments. In cases where the Discharge Visit would occur within 3 days of the End of Study Visit, the respective visits may be done as a single visit.

Table 8: Summary of Required Procedures for Baxalta Clinical Study 241502

5. Perioperative hemostatic efficacy assessment (24 to 72 hours after last perioperative treatment dose of BAX 802)/Discharge Visit/End of Study [EOS] Visit (42 ± 7 days of last dose of BAX 802)

The perioperative hemostatic efficacy assessment will be performed 24 to 72 hours after the last perioperative treatment dose of BAX 802 if subject has not been discharged by then. The Discharge Visit will be performed when the subject is discharged, and the EOS Visit will be performed 42 ± 7 days following the last dose of IP. In cases where the Discharge Visit would occur within 3 days of the EOS Visit, the respective visits will be done as a single visit.

Procedures to be performed for each subject at perioperative hemostatic efficacy assessment/Discharge Visit/EOS Visit:

- Assessment of blood loss
- Assessment of transfusion requirements
  - Review of concomitant medications/non-drug therapies
  - physical examination
  - AE monitoring
  - Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measure body weight)
- Clinical laboratory assessments (Table 10)
- Immunogenicity assays:
  - [redacted]
  - Anti-BHK binding antibody titers

6. Antibody Testing Visit

A visit will be performed between 7 to 14 days after the subject is discharged. Study procedures will be performed as per Table 9 and blood samples will be collected for antibody testing and other tests as per Table 10. De novo or clinically significant increases in antibodies will require a confirmatory blood sample collection 7 to 14 days after the initial positive result.

Procedures to be performed for each subject at Antibody Testing Visit:

- Immunogenicity assays:
  - [redacted] (Note: these will be performed only if at least 72 hours must have elapsed since the previous BAX 802 administration)

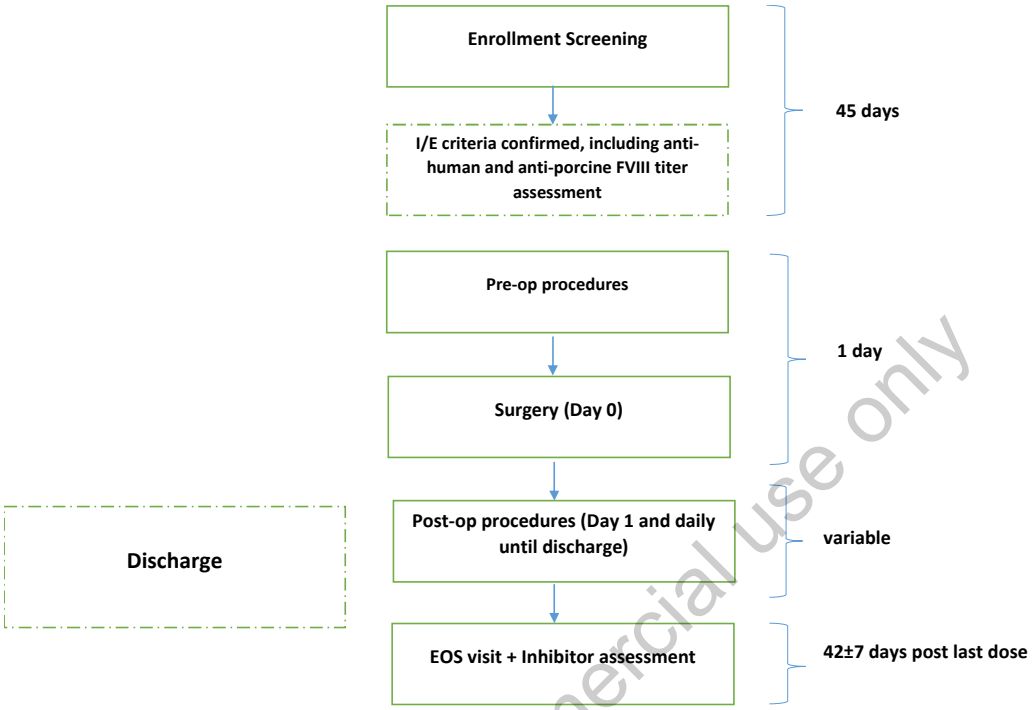
Anti-BHK binding antibody titers

Unrelated Bleeding Episodes During the Postoperative Period:

An unrelated bleeding episode is defined as any bleeding occurring at a different anatomical site than the surgery site during the postoperative period. Refer to Section 11.2.5, Table 9, and Table 10.

20.2 Study Flow Chart

Figure 2: Visit Schedule



20.3 Schedule of Study Procedures and Assessments

Table 9: Schedule of Study Procedures and Assessments

Period	Screening	Preoperative	Intraoperative	Postoperative			End of Study
Visit	**Screening**	**Preoperative procedures**	**Intraoperative procedures**	**Postoperative: Daily procedures; until subject is discharged**	**Day 14 ±3 or Discharge (whichever is earlier) procedures[a]**	**Antibody Testing Visit[b]**	**End of Study Visit[c]/ Discharge procedures[a]**
Time point	**Up to 45 days prior to Day 0**	**Day 0 ~60 to 120 minutes prior to surgery**	**Day 0 During surgery**	**Day 1 and daily thereafter until discharge**	**24 to 72 hours after last perioperative treatment dose of BAX 802 or discharge (whichever is earlier)[j]**	**7 to 14 days after last perioperative treatment dose of BAX 802**	**Discharge day[a] / EOS[c] 42 ± 7 days post-surgery**
Eligibility criteria, including medical history[d]	X						
Prediction of intraoperative blood loss[e]		X					
Medications and non-drug therapies	X	X	X	X	X	X	X
Physical examination	X	X		X[f] (as required)	X	X	X
Adverse events		X	X	X	X	X	X
Laboratory assessments[g]	X	X[i]	X	X[l]	X	X	X
Vital signs[h]	X	X	X	X	X	X	X
Karnofsky Performance Test	X						
Approved FVIII maintenance plan		X					
IP treatment		X (loading dose; Table 5)	X (as required; Table 5)	X (as required; Table 5)			

Table 9: Schedule of Study Procedures and Assessments

Period	**Screening**	**Preoperative**	**Intraoperative**	**Postoperative**			**End of Study**
Visit	**Screening**	**Preoperative procedures**	**Intraoperative procedures**	**Postoperative: Daily procedures; until subject is discharged**	**Day 14 ±3 or Discharge (whichever is earlier) procedures[a]**	**Antibody Testing Visit[b]**	**End of Study Visit[c]/ Discharge procedures[a]**
Time point	**Up to 45 days prior to Day 0**	**Day 0 ~60 to 120 minutes prior to surgery**	**Day 0 During surgery**	**Day 1 and daily thereafter until discharge**	**24 to 72 hours after last perioperative treatment dose of BAX 802 or discharge (whichever is earlier)[j]**	**7 to 14 days after last perioperative treatment dose of BAX 802**	**Discharge day[a] / EOS[c] 42 ± 7 days post-surgery**
Hemostatic Efficacy Assessments (GHEA1, GHEA2, and GHEA3)			GHEA1 at the end of surgery as per Table 2	GHEA2 at 12 to 24 hours (Day 1) as per Table 3	GHEA3 at 24 to 72 hours after the last perioperative treatment dose of study drug is administered or discharge (whichever is earlier), as per Table 4[j]		
Transfusion requirements and blood loss[k]			X	X	X		X
Procedures for Unrelated/Surgical Site Bleeding Episodes During the Postoperative Period (see Sections 11.2.3 and 11.2.5)[m]							
Medications and non-drug therapies			X				
Laboratory assessments			Refer to Table 10				
IP treatment			Refer to Table 6				
Vital signs[h]			X				
Hemostatic Efficacy Assessments			At 24 ±2 hours after the initiation of treatment and at the resolution of bleed (if not resolved within 24 hours) using a 4-point efficacy rating scale (Table 7)				
Transfusion requirements and blood loss[k]			X				

Continued on Next Page

Continued

Key: EOS = End of Study Visit; OR = operating room

[a] In cases where the Discharge Visit would occur within 3 days of the End of Study Visit, the respective visits may be done as a single visit. Procedures differ on Discharge from the other postoperative days only with regard to laboratory assessments (see Table 10).

[b] The Antibody Testing Visit is required. Any de novo (> 0.6 BU) or significantly increased (> 10 BU) results will require confirmatory blood assessments an additional 7 to 14 days later, which is to include the procedures identified here with data recorded as an unscheduled visit.

[c] The End of Study Visit also applies to subjects who withdraw or discontinue prematurely. The EOS visit date must be at least 3 days after the most recent FVIII infusion to ensure that the requirement of a 72-hour washout period is met.

[d] Occurs prior to any study-specific procedures; includes hemophilia history, bleeding episode history, history of aPCC or rFVIIA usage for a year prior to screening.

[e] Preoperative prediction of expected blood loss for a subject with severe hemophilia A with inhibitors and a comparable healthy individual with the same demographic characteristics will be estimated and documented as per Section 11.2.1. This could also be performed days/weeks before the surgery, during the screening period.

[f] Perform physical examination and vital signs (pulse rate, respiratory rate, blood pressure and temperature) on Days 1, 2, 3, and 7 post surgery (if a subject remains admitted).

[g] For laboratory assessments, see Table 10.

[h] Vital signs will include body temperature, pulse rate, blood pressure, respiratory rate, and weight. Blood pressure will be measured when subjects are in the supine position. Height, measured once at Screening, will also be collected. Vital signs will be measured at 30 minutes before and 30 ± 5 minutes after administration of IP.

[i] Within 30 minutes pre-dose and 30 ±5 minutes post-dose for FVIII activity.

[j] If the subject is discharged from surgical facility on the day of the procedure, he should return to the site on Day 1 to perform the postoperative hemostatic efficacy assessment (Day 1 assessment) and the overall peri-operative assessment. In this case, physical examination, vital signs, laboratory assessments, adverse events, and concomitant medications/non-drug therapies must also be assessed. If the subject is discharged from surgical facility after Day 1 but prior to the overall peri-operative assessment, he should return to the site for that assessment as well as the required physical examination, vital signs, laboratory assessments, adverse events, and concomitant medications assessments. See footnote “a” for guidance on the combining of visits and assessments that fall within a 72 hour period.

[k] Record blood loss on a daily basis and at drain removal; record blood product usage, including salvaged blood, packed red blood cells (pRBC), platelets, and other blood products.

[l] Blood draws for FVIII activity determination and hematology should be performed coincident with an early morning dose to the greatest extent possible. Samples for laboratory testing (hematology and clinical chemistry) will be taken daily until discharge from Day 1 through 7 post-surgery and then subsequently once weekly.

[m] May also be collected as an unscheduled visit.

20.4 Clinical Laboratory Assessments

Table 10: Clinical Laboratory Assessments

Period		Screening	Preoperative	Intraoperative	Postoperative			End of Study
Visit		**Screen**	**Prior to surgery**	**Surgery to wound closure (Day 0)**	**Daily hospital visit[a]**	**Perioperative hemostatic efficacy assessment**	**Antibody Testing Visit[b]**	**Discharge, post treatment, and/or End of Study**
Time point		**Up to 45 days prior to Day 0**	**Day 0 ~60 to 120 minutes prior to surgery**	**In OR**	**Day 1 and daily thereafter to discharge**	**24 to 72 hours after last perioperative treatment dose of BAX 802 or discharge (whichever is earlier)[a]**	**7-14 days after last perioperative treatment dose of BAX 802**	**Discharge day[a] / EOS[c] 42 ± 7 days post dose**
FVIII activity (clotting *and* chromogenic assay at central laboratory; clotting assay at local laboratory)	Citrated plasma	C	L and C within 30 minutes before loading dose, then 30 ±5 minutes after loading dose[d]	Optional sampling, as deemed necessary: L and C Also, if subject has excessive or unexplained bleeding	L and C[e]	L and C		L and C
PT and aPTT	Citrated plasma	C and L						
Chemistry[f]	Serum	C	L and C	(L)	L Daily Days 1 to 7	C (L)	C (L)	C (L)
Hematology	Whole blood	C[g]	L[h]	(L)	L Daily Days 1 to 7	C (L)	C (L)	C (L)
Urinalysis	Urine	C				C	C	C
Viral serology[i]	Serum[j]	C						

Table 10: Clinical Laboratory Assessments

Period		Screening	Preoperative	Intraoperative	Postoperative			End of Study
Visit		**Screen**	**Prior to surgery**	**Surgery to wound closure (Day 0)**	**Daily hospital visit[a]**	**Perioperative hemostatic efficacy assessment**	**Antibody Testing Visit[b]**	**Discharge, post treatment, and/or End of Study**
Time point		**Up to 45 days prior to Day 0**	**Day 0 ~60 to 120 minutes prior to surgery**	**In OR**	**Day 1 and daily thereafter to discharge**	**24 to 72 hours after last perioperative treatment dose of BAX 802 or discharge (whichever is earlier)[a]**	**7-14 days after last perioperative treatment dose of BAX 802**	**Discharge day[a] / EOS[c] 42 ± 7 days post dose**
[redacted]	Citrated plasma	C[g]				C	C	C
Anti-BHK binding Antibody titers	Citrated plasma	C				C	C	C
Laboratory Assessments for Unrelated Bleeding/Surgical Site Episodes During the Postoperative Period (see Section 11.2.5)[k]								
FVIII activity (clotting *and* chromogenic assay at central laboratory; clotting assay at local laboratory)	Citrated plasma	Refer to Section 11.2.5 Optional sampling, as deemed necessary: L and C						

Continued on Next Page

Continued

Key: C = central laboratory; EOS = End of Study Visit; L = local laboratory; (L) = local testing optional, to aid in clinical management of patients.

[a] In cases where the Discharge Visit would occur within 3 days of the End of Study Visit, the respective visits will be done as a single visit.

[b] The Antibody Testing Visit is required. Any de novo (> 0.6 BU) or significantly increased (> 10 BU) results will require confirmatory blood assessments an additional 7 to 14 days later, which is to include the procedures identified here with data recorded as an unscheduled visit.

[c] The End of Study Visit also applies to subjects who withdraw or discontinue prematurely.

[d] It is recommended that the surgery starts after FVIII levels have achieved target levels. If FVIII activity post loading dose is close to the target level, a supplement dose of BAX 802 should be administered without further delaying the surgery. If FVIII activity post loading dose is not close to the target level, a supplement dose of BAX 802 should be administered and surgery delayed until FVIII levels have achieved target levels or are in close range.

[e] FVIII activity should be monitored postoperatively as per instructions in Table 5 and Section 8.7.3.3.3.

[f] Sodium, potassium, chloride, bicarbonate, protein, albumin, ALT, AST, total bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, and glucose.

[g] Hematology and antibody testing should be performed during screening at least 2 weeks before the planned surgery day as hematocrit and anti-pFVIII inhibitor titer values are required for loading dose calculation.

[h] Hematology, without differential but including platelets.

[i] HIV-1 and HIV-2 antibody, HAV (IgM and total antibodies), HBsAg, HBsAb, HBcAb, HCV Ab, and parvovirus B19 (IgM and IgG antibodies). CD4 for HIV positive patients and HCV-RNA or HIV-RNA for confirmatory testing of HIV or HCV positive results, respectively.

[j] Citrated plasma for HCV-RNA or HIV-RNA confirmatory testing.

[k] May also be collected as an unscheduled visit.

20.5 Global Efficacy Assessments Scores

Table 11: Combinations of Individual Efficacy Assessments (GHEA1, GHEA2, and GHEA3) and GHEA Score

Individual Assessment Scores (GHEA1, GHEA2, and GHEA3)	GHEA
3 3 3	Excellent
3 3 2	Excellent
3 2 2	Excellent
3 3 1	Good
3 2 1	Good
3 1 1	Good
2 2 2	Good
2 2 1	Good
2 1 1	Fair
1 1 1	Fair
3 3 0	None
3 2 0	None
3 1 0	None
3 0 0	None
2 2 0	None
2 1 0	None
2 0 0	None
1 1 0	None
1 0 0	None
0 0 0	None

20.6 Definitions

20.6.1 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.

20.6.2 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 central nervous system, gastrointestinal, and abdominal hemorrhages see the Guidelines for the management of hemophilia from the WFH.[5,20]

21. REFERENCES

1. Coppola A, Di Capua M, Di Minno MND, et al. Treatment of hemophilia: A review of current advances and ongoing issues. *J Blood Med*. 2010;1:183-195.

2. Janbain M, Leissinger CA, Kruse-Jarres R. Acquired hemophilia A: emerging treatment options. *J Blood Med*. 2015;6:143-150.

3. Mansouritorghabeh H. Clinical and laboratory approaches to hemophilia A. *Iran J Med Sci*. 2015;40(3):194-205.

4. Berntorp E, Shapiro A, Astermark J, et al. Inhibitor treatment in haemophilias A and B: summary statement for the 2006 international consensus conference. *Haemophilia*. 2006;12 Suppl 6:1-7.

5. World Federation of Hemophilia Treatment Guidelines Working Group. Guidelines for the management of hemophilia 2nd Edition. Guidelines for the management of hemophilia 2nd Edition; 2012:80. Web Link: http://www1.wfh.org/publication/files/pdf-1472.pdf

6. Santagostino E, Escobar M, Ozelo M, et al. Recombinant activated factor VII in the treatment of bleeds and for the prevention of surgery-related bleeding in congenital haemophilia with inhibitors. *Blood Rev*. 2015;29 Suppl 1:S9-S18.

7. Valentino LA, Cooper DL, Goldstein B. Surgical experience with rFVIIa (NovoSeven) in congenital haemophilia A and B patients with inhibitors to factors VIII or IX. Haemophilia 589. Vol. 17. Surgical experience with rFVIIa (NovoSeven) in congenital haemophilia A and B patients with inhibitors to factors VIII or IX; 2011:11-579. Web Link: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2010.02460.x/epdf

8. Kempton CL, White GC, II. How we treat a hemophilia A patient with a factor VIII inhibitor. *Blood*. 2009;113(1):11-17.

9. Kasper CK. Effect of prothrombin complex concentrates on factor VIII inhibitor levels. *Blood*. 1979;54:1358-1368.

10. Young G, Sørensen B, Dargaud Y, Negrier C, Brummel-Ziedins K, Key NS. Thrombin generation and whole blood viscoelastic assays in the management of hemophilia: current state-of-art and future perspectives. *Blood*. 2013;121(11):1944-1950.

11. Kempton CL, Abshire TC, Deveras RA, et al. Pharmacokinetics and safety of OBI-1, a recombinant B domain-deleted porcine factor VIII, in subjects with haemophilia A. *Haemophilia*. 2012;18(5):798-804.

12. Mahlangu JN, Andreeva TA, Macfarlane DE, Walsh C, Key NS. Recombinant B-domain-deleted porcine sequence factor VIII (r-pFVIII) for the treatment of bleeding in patients with congenital haemophilia A and inhibitors. *Haemophilia*. 2017;23(1):33-41.

13. Kruse-Jarres R, St Louis J, Greist A, et al. Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A. *Haemophilia*. 2015;21(2):162-170.

14. Brettler DB, Forsberg AD, Levine PH, et al. The use of porcine factor VIII concentrate (Hyate:C) in the treatment of patients with inhibitor antibodies to factor VIII. A multicenter US experience. *Arch Intern Med*. 1989;149(6):1381-1385.

15. Hay CRM, Lozier JN, Lee CA, et al. Safety profile of porcine factor VIII and its use as hospital and home-therapy for patients with haemophilia-A and inhibitors: the results of an international survey. *Thromb Haemost*. 1996;75(1):25-29.

16. Baxter Healthcare Corporation. Package Insert: OBIZUR [antihemophilic factor (recombinant), porcine sequence] lyophilized powder for solution for intravenous injection.;2014. Web Link: https://www.baxter.com/assets/downloads/obizur_pI.pdf

17. Lee CA. The evidence behind inhibitor treatment with porcine factor VIII. *Pathophysiol Haemost Thromb*. 2002;32 Suppl 1:5-8.

18. Kasper C. Diagnosis and Management of Inhibitors to Factors VIII and IX - An Introductory Discussion for Physicians. Vol. 34. Diagnosis and Management of Inhibitors to Factors VIII and IX - An Introductory Discussion for Physicians: World Federation of Hemophilia (WFH); 2004:22. Web Link: http://www1.wfh.org/publications/files/pdf-1178.pdf

19. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, ed. Evaluation of Chemotherapeutic Agents. New York: Columbia University Press; 1949:191-205.

20. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: Communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(22):1935-1939.

22. SUMMARY OF CHANGES

Protocol 241502: Amendment 4, 2017 JUN 28

Replaces: Global Amendment 1, 2016 FEB 03

In this section, changes from the previous version of the Protocol Amendment 1, dated 2016 FEB 03, are described and their rationale is given.

1. *Throughout the document*
   Description of Change: Minor editorial changes to align with most current protocol template version, to update the list of abbreviations, administrative changes to the study team, and for improved clarity and consistency.
   Purpose of Change: For consistency with the current Baxalta protocol template, and to improve clarity and consistency (note: minor edits and deletions that do not substantively change the protocol or are administrative in nature are not individually listed below). Note that changes that are found in the synopsis and more than one section in the body may have minor differences in wording; the common substantive changes are presented here.

2. *Throughout the document*
   Description of Change: Changed analysis of endpoints from "~~Percentage of…~~" to "**Proportion of…**". Changed "at least 10 ~~surgeries~~ in 10 evaluable male subjects" to "at least **12 procedures** in **12** evaluable male subjects"
   Purpose of Change: More suitable statistical and clinical terminology, revised expected enrollment.

3. *Throughout the document*
   Description of Change: Revised formula of loading dose of BAX 802 for major and minor surgeries as follows:
   Major surgery: **[**80 **x body weight** (~~U/~~kg)**]** + **[**body weight (kg) × 40 (1-[HCT[%]/100]) × anti-pFVIII inhibitor titer (BU)**]**
   Minor surgery: **[**50 **x body weight** (~~U/~~kg)**]** + **[**body weight (kg) × 40 (1-[HCT[%]/100]) × anti-pFVIII inhibitor titer (BU)**]**
   Purpose of Change: For greater clarity and accuracy.

4. *Cover page*
   Description of Change: Updated administrative details to reflect new versions (local amendments 2 [Italy] and 3 [Russia] and global amendment 4) and NCT, EudraCT, and IND numbers.
   Purpose of Change: Updated information.

5. *Section 1.1, Study Personnel, Investigator Acknowledgement Signature Page*
   Description of Change: Updated name of Sponsor representative.
   Purpose of Change: Administrative change.

6. *Section 2, Section 12.1.1.2*
   Description of Change: Added text regarding the reporting of SUSARs.
   Purpose of Change: For consistency with the current Baxalta protocol template.

7. *Synopsis*
   Description of Change:
   Added text to Active Product description:
   Dosage form: Injectable **reconstituted solution** of **BAX 802, a recombinant form of porcine factor VIII (rpFVIII) from which the B domain has been deleted**.

   Dosage frequency: **Loading dose, followed by** ~~PRN =~~ as needed **subsequent individualized dosing**.

   Mode of Administration: Intravenous **bolus** infusion **(to the cubital vein is the recommended anatomical site of administration)**.

   Purpose of Change: To align with body of protocol.

8. *Synopsis, throughout the document*
   Description of Change: Changed **12** ~~10 surgeries~~ procedures in ~~10~~ **12** evaluable male subjects
   Purpose of Change: To account for the addition of targeted enrollment of 2 adolescent subjects.

9. *Synopsis, Section 7.3*
   Description of Change: Added Secondary Objective "3.
   To determine the proportion of major surgeries with good or excellent hemostatic score"
   Purpose of Change: To align with endpoints.

10. *Synopsis, Section 7.3*
    Description of Change: Added text to Exploratory Objective [redacted]
    Purpose of Change: Clarification; alignment with FDA request [redacted]

11. *Synopsis, Section 7.4, Section 12.7.3*
    Description of Change: Added exploratory objective and endpoints for [redacted].
    Purpose of Change: To specify exploratory [redacted], and to match objectives and endpoints in the protocol.

12. *Synopsis, Section 7.4*
    Description of Change: Added new exploratory objectives:
    [redacted]:
    Purpose of Change: To specify exploratory objectives for the study.

13. *Synopsis, Sections 7.3, 7.4*
    Description of Change: [redacted]
    exploratory objectives:
    [redacted].
    Purpose of Change: FDA request [redacted]

14. *Synopsis, Section 8.2*
Description of Change: Added text to Study Design as follows:
"This study is a Phase 3, prospective, open-label, uncontrolled, multicenter study to evaluate the efficacy and safety of BAX 802 in at least **12** ~~10 surgeries~~ **procedures** in ~~10~~ **12** evaluable male subjects with CHA with inhibitors to hFVIII who are undergoing major ~~and~~ **or** minor **elective** surgical, dental or other invasive procedures. **The study will be conducted globally and will be divided into 5 periods: Screening, Preoperative, Intraoperative, Postoperative, and End of study.**"
Purpose of Change: Clarification and to align with protocol body; to reflect the new sample size for the study.

15. *Synopsis, Section 8.1*
Description of Change: Added "Subject Selection" section to synopsis, added new text as follows:
At least 5 of the procedures must be major surgeries in 5 evaluable subjects, of which no more than 20% can be dental or other non-operative invasive procedures. Elective surgical procedures will prospectively be defined as major or minor by the Investigator/surgeon, based on the protocol guidance and definitions and in consideration of each subject's characteristics. Emergency surgeries are not in the scope of this study. Subjects may undergo more than 1 surgery or 2 parallel surgeries, such as bilateral knee replacement, however in these cases prior approval by the sponsor is required. In order to evaluate the activity of the product with respect to high-titer or high-responding inhibitors, at least 3 adult subjects with screening anti-hFVIII inhibitory antibody titers of ≥ 5 BU will be enrolled in the study.
Purpose of Change: Clarification and to align with protocol body.

16. *Synopsis, Section 8.3*
Description of Change: Updated study duration and expected completion date.
Purpose of Change: Updated clinical trial conduct information.

17. *Synopsis, Study Schedule, Throughout the document*
Description of Change: Modified planned duration of subject participation to reflect revised End of Study Visit timing (42 ± 7 days after last dose).
Purpose of Change: To align with changes to study schedule.

18. *Throughout the document*
Description of Change: Changed 3rd GHEA (GHEA3) score assessment from Day 14/discharge to **discharge or within** 24 to 72 hours after the last perioperative treatment dose of BAX802.
Purpose of Change: To provide a more meaningful post-operative GHEA assessment.

19. *Synopsis, Section 8.4.1, Section 11.1*
Description of Change: Added text "The primary outcome measure is the **proportion of all surgical, dental, or other invasive procedures with a "good" or "excellent" response as measured by** GHEA score, which is composed of 3 individual ratings:"
GHEA1: Assessment of intraoperative **(Day 0)** hemostatic efficacy of BAX 802 performed by the operating surgeon **at the end of surgery**
GHEA2: Assessment of postoperative hemostatic efficacy of BAX 802 at postoperative Day 1 ~~approximately~~ **(postoperative period) from end of surgery to and** 24 **±6** hours ~~after~~ **post-**surgery performed by the operating surgeon**. If a patient is discharged < 24 hours following surgery, then the 3rd GHEA hemostatic efficacy assessment may require a return visit the following day.**
GHEA3: Assessment of overall perioperative hemostatic efficacy of BAX 802 at ~~Day 14 or~~ discharge **related to the perioperative procedure or within 24 to 72 hours after the last perioperative treatment dose of BAX 802 if hospitalization is prolonged for reasons other than perioperative procedures** (whichever is earlier), performed by the Investigator**, and where possible, by the operating surgeon. Assessment by both is strongly recommended. In cases where there are differing assessments, the Investigator's assessment will be used.**
The scores of each of the 3 individual ratings described above (**GHEA1, GHEA2, GHEA3**), will be added together to form a GHEA score. **Hemostatic efficacy success is defined as an "excellent" or "good "outcome for ≥ 70% of hemostatic efficacy assessments.**

Purpose of Change: Addition of pre-specified success criterion, revised assessment time, and specification of individuals making the assessment at request of FDA.

20. *Synopsis, Section 8.4.1, Section 13.3*
Description of Change: Added text to statistical analyses section to clarify that "**For surgeries with up to two missing hemostatic assessments that did not necessitate rescue therapies, the rating of "fair" will be imputed for these missing data. These surgeries will be included in the FAS**".
Purpose of Change: to clarify how outcomes will be measured and missing data will be addressed.

21. *Synopsis, Section 8.4.2.1*
Description of Change: modified first secondary outcome measure (expected **intra- and post-operative** blood loss) to specify the comparative blood loss in healthy individuals "**with similar demographic characteristics**". Added text to specify that Intraoperative is "**from start of surgery** until the end of surgery" and that Postoperative Day 1 is "**from end of surgery**" to approximately 24 hours **±6 hours** after surgery.
Purpose of Change: To improve clarity for Investigators.

22. *Synopsis, Section 8.4.2.1*
Description of Change: added new secondary outcome measure:
"**2. Proportion of major surgeries with good or excellent hemostatic outcome together with its 2-sided 95% confidence interval**"
Purpose of Change: Additional efficacy analysis requested by FDA.

23. *Synopsis, Section 8.4.2.1*
Description of Change: [redacted] Exploratory Outcomes: "[redacted]."
Purpose of Change: [redacted] as suggested by FDA.

24. *Synopsis, Section 8.4.2, Section 11.1*
Description of Change: Addition of new exploratory outcome measure: "[redacted]".
Purpose of Change: The original secondary objective [redacted], and text modified for clarity.

25. *Synopsis, Section 8.4.2.2*
Description of Change: added text specifying that **IgG and IgM** inhibitory and binding antibodies will be assessed during the study.
Purpose of Change: Clarification.

26. *Synopsis, Section 8.4.3*
Description of Change: Added Exploratory Outcomes:
[redacted]
Purpose of Change: [redacted]

27. *Synopsis, Section 9.1*
Description of Change: Revised Inclusion Criterion 2 to specify that only male subjects 12 to 75 years of age and under will be enrolled, Added text to Inclusion Criterion 8 specifying that "Subject is hepatitis C virus negative (HCV-) by antibody or polymerase chain reaction (PCR) testing; or HCV+ with chronic stable hepatitis disease. **If positive, the antibody titer will be confirmed by PCR.**"
Purpose of Change: For consistency within the protocol regarding ineligibility of female patients. To address those potential patients who may have been on long-term treatment with bypassing agents and whose levels of inhibitors would therefore be lower, but who should still be considered eligible for the study as they are patients with inhibitors who can no longer be treated with human FVIII. To include subjects with high-titer or high-responding inhibitors and to increase maximum age of study subjects at request of FDA; edits for clarification and consistency.

28. *Synopsis, Section 9.1*
Description of Change: Revised Inclusion Criterion 3 to allow for assent of adolescent subjects: "Subject has provided signed informed consent **(and assent for adolescent subjects, as applicable) in accordance with local regulatory requirements**"
Purpose of Change: To allow for enrollment of adolescent subjects.

29. *Synopsis, Section 9.2*
Description of Change: Removed weight exclusion criterion. Added new Exclusion Criterion 9 **Subject has an ongoing or recent (within previous 3 months) thrombo-embolic disease, fibrinolysis or disseminated intravascular coagulation (DIC)**.
Purpose of Change: Weight restriction removed at request of FDA. New exclusion criterion added to reflect current safety profile of IP. Other minor edits to exclusion criteria as appropriate for clarity and consistency.

30. *Synopsis, Section 13.1*
Description of Change: Revised text to reflect enrollment of adolescent subjects.
Sample Size and Power Calculations
The **total** sample size ~~of surgeries~~ **for the study is 12 evaluable subjects, which includes** at least ~~10~~ **12 procedures** in **12** ~~10~~ evaluable male subjects (at least 5 major surgeries in 5 evaluable subjects) **and at least 2 adolescents (≥ 12 to < 18 years old). The sample size**, as defined in the protocol, was chosen to provide sufficient evidence of safety and effectiveness for this indication and is not based on statistical considerations.
Evaluable subjects are defined as subjects who met all study entry criteria and who had **at least one** ~~all the 3~~ hemostatic efficacy assessment~~s~~ as per Section 8.4.1.
Purpose of Change: To align with changes to other parts of the protocol regarding sample size. To better define evaluable subjects.

31. *Synopsis, Section 13.4.1, Tables 8, 9, and 10*
Description of Change: Changed 3rd GHEA assessment from Day 14 to discharge or within **24 to 72 hours after last perioperative dose** (whichever is earlier) and would be assessed by both surgeon and PI and added the following text:
…
The primary efficacy measure will be the overall assessment of hemostatic efficacy assessed intraoperatively and postoperatively by the surgeon at postoperative Day 1 (~~ie, the day following the day~~ **postoperative period, i.e., from end** of surgery ~~up to 24~~**to between 12 and 24** hours post-surgery) and perioperatively at ~~postoperative Day 14 visit~~ **24 to 72 hours after the last perioperative treatment dose of BAX 802 is administered** or discharge (whichever is earlier) **by the surgeon and by the Investigator (hemophilia physician), and where possible, by both the Investigator and the operating surgeon (assessment by both is strongly recommended), and,** and will be ~~summarized~~ **the sum of intraoperative, postoperative, and perioperative** ~~by the~~ GHEA score**s as** ~~and~~ rated "excellent", "good", "fair" ~~and~~ **or** "none". **If discharge is delayed for a reason other than**

surgery related bleeding (e.g., pneumonia), an assessment at 24 to 72 hours after last perioperative treatment dose of BAX 802 will ensure that the overall perioperative assessment is completed close to the last administered study drug dose. Wherever possible (except for intraoperative assessment), bleeding should be assessed by both operating surgeon and Investigator. To achieve the hemostatic efficacy success ~~will be defined as a rating of~~ **criteria, the study needs to achieve a ≥ 70% rate of hemostatic efficacy assessments with an** "excellent ~~and/~~" **or** "good~~.~~" **outcome in at least 12 procedures.**

…

~~Owing~~**Due to** the possibility of **a subject undergoing** multiple surgeries ~~per subject~~, **the statistical** ~~entity on which~~**analysis of** the primary outcome measure will be reported ~~is~~**on** the **by-**surgery **level (i.e., not by the number of subjects). In cases where two or more surgical procedures are performed in the same intraoperative settings (under the same anesthesia e.g., bilateral knee replacement) the surgery will be counted as one surgery. Blood loss assessment from those surgeries will be assessed as one. In the event that the subject is planning to have additional surgery in the future, they will need to complete the study and be re-screened again to ensure that they continue to meet the eligibility criteria.**

…

Point estimates and corresponding 2-sided exact **Clopper-Pearson** confidence intervals (CIs) at the ~~90~~ **95**% confidence level will be calculated for the rate of hemostatic efficacy assessments with excellent/good outcome **for descriptive purposes**.

…

The proportion of major surgeries with hemostatic success will be reported along with exact 95% CIs. A treatment success will be defined as a rating of excellent or good.

…

A sensitivity analysis based on the first surgery will be performed if more than 20% of subjects have multiple surgeries.

Purpose of Change: Changed 2-sided CIs from 90% to 95%, added prospective sensitivity analysis in case > 20% of subjects have multiple surgeries, added new secondary outcome measure "Proportion of major surgeries with good or excellent hemostatic score" to align with changes to study assessments and addition of sensitivity analysis per FDA request.

32. *Section 6.2*

Description of Change: Revised text as follows: "Overall, CHA accounts for about 80% of hemophiliacs. It affects all ethnic populations and its prevalence varies among different countries, but is estimated at a rate of 3 to 20 cases per 100,000 population. The World Federation of Hemophilia (WFH) has estimated the total number of hemophilia cases at about 500,000 ~~universally~~**worldwide**, of which one-third are diagnosed. The tendency to bleed in these subjects correlates with the plasma level of FVIII. This lifelong disorder has 3 clinical phenotypes (severe, moderate, and mild) that correlate with FVIII levels in plasma (< 1%, 1 to 5%, and 5 to ~~30~~**40**%, respectively)"

Purpose of Change: Reworded for clarity; correction.

33. *Section 6.3; Section 8.1*

Description of Change: Added text specifying that of the at least 5 major surgeries in 5 evaluable subjects in the study, no more than 20% could be dental or other non-operative invasive procedures. Added text "**In order to evaluate the activity of the product with respect to high-titer or high-responding inhibitors, at least 3 adult subjects with screening anti-hFVIII titers of ≥ 5 BU will be enrolled in the study**".

Purpose of Change: To ensure that the surgical procedures captured in this study are representative of the full spectrum of possible surgeries and to include subjects with high-titer or high-responding inhibitors at request of FDA.

34. *Section 6.4.2*

Description of Change: Added enrollment numbers for previous clinical trials. Revised text as follows:

"At the time of OBIZUR® marketing approval, the clinical trial data indicated that rpFVIII was well tolerated and had demonstrated effectiveness in the control of bleeding in study subjects. **Cumulatively (patient exposure from 01 Oct 2014 through 30 Apr 2016), approximately 16,424,000 units (U) of OBIZUR® were sold worldwide. Median (range) treatment dose per bleeding episode was 94,500 (35,256 to 182,700), and the estimated number of patient-years worldwide to OBIZUR® was approximately 357.6 (179.8 to 931.6) (PBRER [DLP 31Oct2016]).** As of ~~2015 December 31~~**11 Nov 2017**, there have been ~~4~~**20** post-marketing ~~spontaneous~~serious **case reports with 36** ~~adverse event reports.~~**AEs. No adverse reactions other than those observed in clinical trials have been observed in the post marketing setting.** The reports were considered ~~possibly associated and~~ consistent with the known safety profile of OBIZUR®.[14]"

Purpose of Change: Clarification, and to reflect updated safety information for study drug.

35. *Section 8.2*
Description of Change: Added text specifying geographic scope of study.
Purpose of Change: Requested by FDA.

36. *Section 8.2.1.1, Section 8.2.1.2*
Description of Change: Added text specifying that extraction of fewer than 3 teeth (or third molar) would be considered minor surgery.
Purpose of Change: To improve clarity.

37. *Section 8.2.2*
Description of Change: Deletion of the following text: "~~This regimen for loading dose of BAX 802 proposed for Study BAX 802 Surgery takes into account the titer of anti-pFVIII inhibitors~~".
Purpose of Change: Editorial change.

38. *Section 8.4.1*
Description of Change: Added text specifying that surgeries with one or two missing hemostatic assessments that did not necessitate rescue therapies will have the rating of "fair" imputed for these missing data. These surgeries will be included in the FAS.
Purpose of Change: To improve clarity.

39. *Section 8.4.1*
Description of Change: Added text as follows: "**Prior to the surgery, the surgeon/Investigator will predict the estimated volume (in mL) of the expected 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 and from completion of the procedure until approximately 24 hours post-surgery and for the overall perioperative period (see Section 11.2.1).**"
Purpose of Change: To clarify the recording of predicted blood loss.

40. *Section 8.4.1, Tables 2 through 4*
Description of Change: Added text specifying that rescue therapy includes use of other FVIII products.
Purpose of Change: To improve clarity.

41. *Section 8.4.1, Tables 2, 3 and 4*
Description of Change: In all 3 tables, added text specifying GHEA assessment number.
Table 2 – changed 1st row as follows: At the **end of surgery**~~time of discharge from the OR~~, the operating surgeon will assess the intraoperative hemostatic efficacy
Table 3 – changed 1st row as follows: On postoperative Day 1 **(24 ± 6 hours post-surgery)**, the operating surgeon will assess the postoperative hemostatic efficacy ~~by the operating surgeon~~
Table 4 – changed 1st row as follows: At ~~Day 14 or~~ discharge **or within 24 to 72 hours after the last perioperative treatment dose of BAX 802** (whichever is earlier), ~~a hematologist will assess~~ the postoperative efficacy **assessment will be performed by the Investigator, and where possible, and where possible, by both the Investigator and the operating surgeon**

Purpose of Change: To align with changes elsewhere in the protocol regarding timing of GHEA assessments.

42. *Section 8.6, Section 15.4*
Description of Change: Replaced internal Safety Monitoring Committee with external data safety monitoring board (DSMB).
Purpose of Change: Requested by FDA.

43. *Section 8.7*
Description of Change: Added detailed description of IP as follows:
"**The IP, BAX 802, is a recombinant purified form of porcine factor VIII (rpFVIII) from which the B domain has been deleted and replaced with a 24 amino acid linker. Recombinant pFVIII (BAX802) is expressed as a glycoprotein by a genetically engineered BHK cell line. The molecular weight of rpFVIII is approximately 175 kDa (based on its 1448 amino acid sequence) and has 86% pair-wise sequence homology with hFVIII.**"
Purpose of Change: To improve comprehensiveness of IP description.

44. *Section 8.7.1*
Description of Change: Added text describing IP storage instructions as follows:
"**BAX 802 should be kept refrigerated at 2°C to 8°C (36°F to 46°F). The following precautions should be taken:**
--Do not freeze
--Do not use if frozen, even if it has been thawed
--Do not use beyond the expiration date printed on the carton or vial
--Do not use after > 3 hours of reconstitution."
Purpose of Change: Added to clarify storage instructions for sites.

45. *Section 8.7.2*
Description of Change: Added text describing anatomical location of infusion:
"The reconstitution procedures for BAX 802 are detailed in the Pharmacy Manual. Reconstituted BAX 802 should be kept and administered at room temperature and must be administered within 3 hours of reconstitution.
BAX 802 will be administered as an intravenous **bolus** infusion **to the cubital vein** per the dosing schema for major and minor surgeries (Table 5)."
Purpose of Change: Added to clarify IP administration instructions for sites.

46. *Section 8.7.3.3.1*
Description of Change: Added text clarifying that the loading dose of BAX 802 should be **(administered approximately 1 to 2 hours prior to the surgery)**
Purpose of Change: Added to clarify IP dosing instructions for sites.

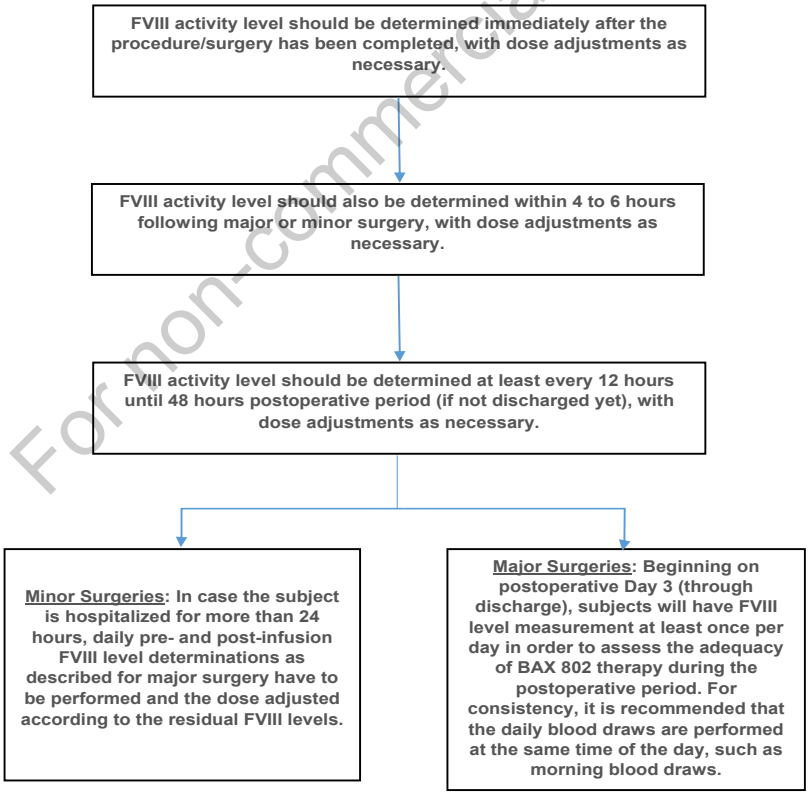
47. *Section 8.7.3.3.2*
Description of Change: Added text clarifying dosing procedures for BAX 802 as follows:
~~In case of major surgery,~~ **The recommended** FVIII target level is ≥ 80% for major surgeries/procedures and ≥ 50% for minor surgeries/procedures.
It is recommended that the surgery starts after FVIII levels have achieved target levels. ~~If~~ **However, if** FVIII activity post loading dose is close to the target level, a **supplemental** dose of BAX 802 should be administered without further delaying the surgery**, based on Investigator's judgement. Close to the target for major and minor surgeries will be defined as levels of ≥ 70% for major and ≥ 40% for minor surgery respectively. This is 10% from the target, which is considered a normal variation.**
If FVIII activity post loading dose is not close to the target level, a supplement dose of BAX 802 should be administered and surgery delayed until FVIII levels have achieved target levels or are in close range.

Subjects will receive subsequent doses of BAX 802 in order to achieve the FVIII target level (See Table 5). All subsequent dosing of BAX 802 should be preceded by measurement of residual FVIII levels and dose adjustments must be based on the most recent residual FVIII activity levels.
Purpose of Change: Added to clarify IP dosing instructions for sites.

48. *Section 8.7.3.3.3, Section 8.7.3.3.4*
Description of Change: Revised section by reordering text, adding diagram, removing text instructions for monitoring of FVIII and postoperative dosing, and adding text addressing the timing of discontinuation of postsurgery IP due to operational issues at site.

Added:
All surgeries/procedures are to have FVIII levels monitored per the diagram in Figure 1:

Figure 1: Postoperative FVIII Monitoring



More frequent monitoring of FVIII activity is advised in subjects who have baseline anti-pFVIII inhibitor titers of > 0.6 BU.
All subsequent dosing of BAX 802 must be preceded by measurement of residual FVIII levels pre-dose and FVIII level measurement 30 ±5 minutes post-dosing.
…

The following text was deleted in two places:

~~Note:~~

- ~~FVIII activity level should be determined immediately after the procedure/surgery has been completed, with dose adjustments as necessary.~~
- ~~FVIII activity level should also be determined within 4 to 6 hours following major surgery, with dose adjustments as necessary.~~
- ~~Following this, FVIII activity level should be determined at least every 12 hours till 48 hours postoperative period (if not discharged yet), with dose adjustments as necessary.~~
- ~~Beginning on postoperative Day 3 (through discharge), subjects will have FVIII level measurement at least once per day in order to assess the adequacy of BAX 802 therapy during the postoperative period. For consistency, it is recommended that the daily blood draws are performed at the same time of the day, such as morning blood draws.~~

~~More frequent monitoring of FVIII activity is advised in subjects who have baseline anti-pFVIII inhibitor titers of >5 BU.~~
~~ALL subsequent dosing of BAX 802 must be preceded by measurement of residual FVIII levels pre-dose and FVIII level measurement 30 ±5 minutes post-dosing.~~

New text added: "**If a subject is discharged or cannot be continued on IP at the study site, (e.g., because the clinic is closed on weekends), study participation should end at the time of hospital discharge and follow-up treatment, if any, should proceed with SOC products as per Investigator's discretion.**

Note: IP (BAX 802) will not be dispensed to the subjects for in-home use."

Purpose of Change: Added to improve readability of section, and to address postsurgical use of BAX 802.

49. *Section 9.3*
Description of Change: Deleted noncompliance as reason for withdrawal text.
Purpose of Change: Not applicable in this study where IP is administered in a surgical setting.

50. *Section 10.2*
Description of Change: Changed site numbers from 2 to 3 digits.
Purpose of Change: To align with current Baxalta standards.

51. *Section 10.4.1*
Description of Change: Modified text to reflect revised End of Study Visit timing (42 ± 7 days after last dose):
Discharge Visit will be performed when the subject is discharged and the~~. The~~ End of Study Visit will be performed 42 ~~to 49~~**± 7** days following the completion of the surgical procedure. In cases where the Discharge Visit would occur within 3 days ~~of either the Day 14 or~~ the End of Study Visit, the respective visits ~~will~~can be done as a single visit. **Sites must make every effort to complete 3 independent GHEA assessments for both minor and major procedures, preferably allowing for as much time as possible to pass between assessments within the windows specified in this protocol.**

Purpose of Change: To align with changes to study schedule.

52. *Section 10.4.2*
Description of Change: Modified text to reflect revised Antibody Testing Visit.
"10.4.2 ~~Optional~~ Antibody Testing Visit

~~Whenever feasible, a~~**A** visit will be performed between 7 to 14 days after the ~~subject is discharged.~~**last perioperative dose of BAX 802**. Study procedures will be performed as per Table 9 and blood samples will be collected for antibody testing~~s~~ and other tests as per Table 10. ~~This visit is optional.~~

Purpose of Change: To reflect that the 7 to 14 day antibody assessment is to be required for all subjects.

53. *Section 10.4.3*
Description of Change: Added new section for "Unscheduled Visits".
Purpose of Change: To align with changes elsewhere in the amended protocol.

54. *Section 10.5*
Description of Change: Added text to clarify that certain prohibited concomitant medications may be used as rescue drugs:

The following medications are not permitted **before discharge (unless used as rescue medications or used to treat unrelated/surgical site bleeding episodes as specified below)**:

…

Hemophilia inhibitor bypassing therapy (recombinant factor VIIa [NovoSeven] within 3 hours or activated prothrombin complex concentrate [aPCC (FEIBA)] within ~~6~~ **12** hours prior to initial BAX 802 administration) unless used as a rescue medication (Section 10.5) after failure/study withdrawal **or used to treat unrelated/surgical site bleeding episodes (Section 11.2.3)**

Purpose of Change: To clarify rescue medication use.

55. *Section 11.2.1*
Description of Change: Added text to clarify recording of expected blood loss prior to surgery:
The observed versus predicted **(recorded prior to surgery)** operative blood loss will be described for the period from initiation of the intervention to discharge or ~~14 days~~ **24 to 72 hours** after the ~~intervention~~ **last perioperative treatment dose of BAX 802** (whichever is first), as applicable
….
"**The expected normal/average, and maximal blood loss and transfusion requirement estimate will be timestamped into the source documentation and/or blood loss form prior to surgery into the CRF. No changes will be allowed to these estimates after the surgery.**"

Purpose of Change: Per FDA request.

56. *Section 11.2.3*
Description of Change: Added text to clarify bleeding episodes as follows:
Bleeding episodes will be classified as follows:

Unrelated bleeding episodes: an unrelated bleeding episode is defined as any bleeding occurring at a different anatomical site than the surgery site during the postoperative period. Treatment of such events should be performed as per Section 11.2.5 and Table 6.

Surgical site bleeding episodes: Surgical site bleeding episodes are any bleeding at the surgical/procedure site which occurs after discharge (related to the perioperative procedure) or 72 hours after the last perioperative treatment dose of BAX 802 (if hospitalization is prolonged for reasons other than perioperative procedures), whichever is earlier.
These bleeding episodes will be treated as follows:

If these unrelated bleeding episodes or surgical site bleeding episodes occur during the subject's stay in hospital, it is recommended that subjects are treated with BAX 802. BAX 802 will be dosed as per the most recent residual FVIII activity level and clinical judgment using the dosing regimen provided in Table 6 [Required dose = body weight (kg) × desired FVIII rise (U/dL or % of normal)]/1.2 (U/kg per U/dL)]. All subsequent dosing of BAX 802 should be preceded by measurement of residual FVIII levels and dose adjustments must be based on the most recent residual FVIII activity levels.

If these unrelated bleeding episodes or surgical site bleeding episodes occur after the subject has been discharged, subjects may be treated with BAX 802 or SOC, as per Investigator's discretion.

An unscheduled visit could be performed for management of bleeding episodes.

Note: IP (BAX 802) will not be dispensed to the subjects for in-home use.

Purpose of Change: To clarify bleeding episodes.

57. *Section 11.2.5*
Description of Change: Added text regarding bleeding episodes at the surgical site and to clarify possible use of IP to treat unrelated bleeding episodes as follows:
11.2.5 Hemostatic Efficacy Rating for Treatment of Unrelated/Surgical Site Bleeding Episodes
An unrelated bleeding episode is defined as any bleeding occurring at a different anatomical site than the surgery site during the postoperative period. Surgical site bleeding episodes are any bleeding at the surgical/procedure site which occurs after discharge (related to the perioperative procedure) or 72 hours after the last perioperative treatment dose of BAX 802 (if hospitalization is prolonged for reasons other than perioperative procedures), whichever is earlier. These bleeding episodes will be treated as per Section 11.2.3.

If subject is treated with BAX 802 for unrelated bleeding episodes **or surgical site bleeding episodes**, the subject will rate the severity (minor, moderate, or major) of the bleeding episode and will rate the overall treatment response at 24 ±2 hours after the initiation of treatment and at the resolution of bleed (if not resolved within 24 hours) using a 4-point efficacy rating scale (Table 7). **Data could be collected as an unscheduled visit.**"

…

Table 7: Efficacy Rating Scale for Treatment of Unrelated/**Surgical Site** Bleeding Episodes

Purpose of Change: To clarify that BAX 802 may be used to treat unrelated bleeding episodes at the study site per the Investigators' judgment.

58. *Section 12.1.1.1.1*

Description of Change: Added text to SAE section, added new section for Inhibitory Serious Adverse Events:

The confirmed development of de-novo anti-pFVIII inhibitory antibodies or increases of >10 BU in pre-existing titers of anti-pFVIII inhibitory antibodies (See Section 12.1.1.1.1)

Section 12.1.1.1.1 Inhibitory Serious Adverse Events

The development of de-novo anti-pFVIII inhibitory antibodies (≥ 0.6 BU) must be confirmed with a second blood draw 7 to 14 days after the initial confirmed positive de novo result (or repeat testing of original sample if a second draw is not possible). Confirmation of de novo inhibitory antibodies or a confirmed increase of > 10 BU in pre-existing titers of anti-pFVIII inhibitory antibodies must be reported as a SAE within 24 hours, and followed up.

Increases in pre-existing titers of anti-pFVIII inhibitory antibodies will require a second confirmatory test 7 to 14 days after the initial confirmed positive increase (or repeat testing of original sample if a second draw is not possible). If the protocol-defined significant increase (> 10 BU) is confirmed it will be reported as an SAE.

Safety will be further monitored by the Investigator and medical monitor to evaluate the clinical significance of the inhibitor level. Although the development of, or increase in, anti-rpFVIII inhibitory antibody titers may not necessarily indicate a failure of response to BAX 802, the inhibitor levels and patient response will be closely monitored and an alternative therapy will be considered for lack of efficacy, if applicable.

Purpose of Change: Per FDA request.

59. *Section 12.1.1.2*
Description of Change: Added new section for SUSARs:
12.1.1.2 Suspected Unexpected Serious Adverse Reaction

Any suspected adverse reaction to study treatment that is both serious and unexpected.

The event(s) must meet all of the following:
--Suspected adverse reaction
--Serious
--Unexpected
--Assessed as related to study treatment

Once determined to meet the criteria for a SUSAR, an SAE should be submitted to regulatory agencies expeditiously.

Purpose of Change: To align with the current Baxalta protocol template.

60. *Section 12.1.2.3*
Description of Change: Deleted references to EDC and eCRFs.
Purpose of Change: This study will use paper CRFs.

61. *Section 12.7.3*
Description of Change: Revised text as follows:
A central reference laboratory will perform assays (anti-pFVIII, anti-hFVIII, and anti BHK) on samples taken at ~~Screening, Day 14 or discharge (whichever is earlier), and End of Study Visits.~~the time indicated in Table 9 and Table 10.

~~Binding antibodies to pFVIII, hFVIII, and BHK, will be measured using ELISA.~~ **Binding antibodies to human and porcine FVIII (both IgG and IgM) and binding antibodies to BHK proteins will be analyzed using validated ELISAs using a multi-tiered approach consisting of screening assay, titer determination and confirmation of specificity.** [redacted]

Purpose of Change: To clarify immunogenicity assessments.

62. Section 12.8
Description of Change: Added text specifying that vital signs will be collected at unscheduled visits.
Purpose of Change: To improve clarity and consistency.

63. Section 12.10
Description of Change: Added text specifying that samples will be collected for anti-pFVIII, anti hFVIII, and anti-BHK binding antibodies, and added reference to new Inhibitory SAE Section 12.1.1.1.1.
Purpose of Change: To improve clarity and to align with changes to other parts of the protocol.

64. 13.4.3 Exploratory Outcome Measures (new section)
Description of Change: Added text to address exploratory outcome measure analyses.

[redacted]:

[redacted]:

[redacted]:

[redacted]:

Further details will be included in the SAP.

Purpose of Change: To align with changes to other parts of the protocol regarding exploratory analyses.

65. *Section 13.5*
    Description of Change: Removed interim analysis text.
    Purpose of Change: No interim analyses are planned for this study.

66. *Section 20, Table 8*
    Description of Change: Revised to reflect changes in study procedures as described in the protocol body.
    Purpose of Change: Consistency with other changes.

67. *Section 20, Table 9*
    Description of Change: Revised table reflect changes in study procedures as described in the protocol body.
    Purpose of Change: Consistency with other changes.

68. *Section 20, Table 10*
    Description of Change: Revised table reflect changes in study procedures as described in the protocol body.
    Purpose of Change: Consistency with other changes.

69. *Section 21*
    Description of Change: Deleted reference #14.
    Purpose of Change: New Obizur safety report will be referenced as a footnote and not an end of text reference.

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: BAX 802

STUDY TITLE: A Phase 3, Multicenter, Single-arm, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX 802) in Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures

PROTOCOL IDENTIFIER: 241502

CLINICAL TRIAL PHASE 3

AMENDMENT 4: 2017 JUN 28

Replaces: GLOBAL AMENDMENT 1: 2016 FEB 03

OTHER ID(s)
NCT Number: NCT02895945
EudraCT Number: 2015-005521-39
IND NUMBER: BB-IND 014798

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 Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: BAX 802

STUDY TITLE: A Phase 3, Multicenter, Single-arm, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX 802) in Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures

PROTOCOL IDENTIFIER: 241502

CLINICAL TRIAL PHASE 3

AMENDMENT 4: 2017 JUN 28

Replaces: GLOBAL AMENDMENT 1: 2016 FEB 03

OTHER ID(s)
NCT Number: NCT02895945
EudraCT Number: 2015-005521-39
IND NUMBER: BB-IND 014798

By signing below, the Investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD
[redacted], Clinical Programs and Therapeutic Area Head
Baxalta Innovations GmbH

CLINICAL STUDY PROTOCOL

PRODUCT: BAX 802

STUDY TITLE:
A Phase 3, Multicenter, Single-arm, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX 802) in Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures

STUDY SHORT TITLE: BAX 802 in Congenital Hemophilia A with Inhibitors

PROTOCOL IDENTIFIER: 241502

CLINICAL TRIAL PHASE 3

AMENDMENT 6: 2017 DEC 14

Replaces:

AMENDMENT 4: 2017 JUN 28

ALL VERSIONS:
Amendment 6: 2017 DEC 14
Amendment 5 (Russia): 2017 AUG 08
Amendment 4: 2017 JUN 28
Amendment 3 (Russia): 2017 FEB 07
Amendment 2 (Italy): 2016 AUG 22
Amendment 1: 2016 FEB 03
Original: 2015 SEP 30

OTHER ID(s)
NCT Number: NCT02895945
EudraCT Number: 2015-005521-39
IND NUMBER: BB-IND 014798

Study Sponsor(s):

Baxalta US Inc.
One Baxter Way
Westlake Village, CA 91362,
UNITED STATES

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna,
AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted], Clinical Programs and Therapeutic Area Head
Baxalta Innovations GmbH

1.2 Study Organization

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

2. SERIOUS ADVERSE EVENT REPORTING

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

ALL SAEs, INCLUDING SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARs), MUST BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT. SAEs MUST ALSO BE RECORDED ON THE ADVERSE EVENT CASE REPORT FORM (CRF).

Drug Safety contact information: see SAER form

Refer to SAE Protocol Sections and the study team roster for further information.

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

- AEs, Section 12.1
- SAE, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- Assessment of AEs, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	BAX 802
Name(s) of Active Ingredient(s)	Recombinant Porcine Factor VIII (rpFVIII)
CLINICAL CONDITION(S)/INDICATION(S) Congenital hemophilia A (CHA) patients with inhibitors to Factor VIII (FVIII) undergoing surgical and other invasive procedures	
PROTOCOL ID	241502
PROTOCOL TITLE	A Phase 3, Multicenter, Single-arm, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX 802) in Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures
Short Title	BAX 802 in CHA with Inhibitors
STUDY PHASE	Phase 3
PLANNED STUDY PERIOD	
Initiation	2016, DEC
Primary Completion	2019, MAR
Study Completion	2019 MAR
Duration	Approximately 28 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose To evaluate the efficacy and safety of BAX 802 in males with CHA with inhibitors who are undergoing major or minor elective surgical, dental, or other invasive procedures.	
Primary Objective To evaluate the perioperative hemostatic efficacy of BAX 802 in male subjects with CHA with inhibitors to human factor VIII (hFVIII) undergoing major or minor elective surgical, dental, or other invasive procedures as determined by the Global Hemostatic Efficacy Assessment (GHEA) score.	
Secondary Objectives 1. To determine the safety of BAX 802 used in the perioperative setting by assessing: • The development of and change in titer of anti-porcine FVIII (pFVIII) and anti-hFVIII antibodies (binding and neutralizing), and development of binding antibodies to baby hamster kidney (BHK) proteins • The occurrence of thrombo-embolic events and/or allergic reactions to BAX 802 • The occurrence of adverse events (AEs) related to BAX 802	

- The occurrence of clinically significant changes in vital signs and routine laboratory parameters related to BAX 802

2. To determine the intraoperative, postoperative, and overall perioperative blood loss, compared to the estimated volume of expected average and maximum blood loss in a comparable healthy individual as predicted preoperatively by the Investigator/surgeon
3. To determine the proportion of major surgeries with good or excellent hemostatic score
4. To determine the daily and total weight-adjusted administration of BAX 802 per subject

Exploratory objectives

[redacted]

STUDY DESIGN

Study Type/ Classification/ Discipline	Efficacy and Safety
Control Type	No control arm
Study Indication Type	Treatment
Intervention model	Single-group
Blinding/Masking	Open-label
Study Design	This study is a Phase 3, prospective, single-arm, open-label, uncontrolled, multicenter study to evaluate the efficacy and safety of BAX 802 in at least 12 procedures in 12 evaluable male subjects with CHA with inhibitors to hFVIII who are undergoing major or minor elective surgical, dental or other invasive procedures. The study will be conducted globally and will be divided into 5 periods: Screening, Preoperative, Intraoperative, Postoperative, and End of study.
Subject Selection	At least 5 of the procedures must be major surgeries in 5 evaluable subjects, of which no more than 20% can be dental or other non-operative invasive procedures. Elective surgical procedures will prospectively be defined as major or minor by the Investigator/surgeon, based on the protocol guidance and definitions and in consideration of each subject's characteristics. Emergency surgeries are not in the scope of this study.

	Subjects may undergo more than 1 surgery or 2 parallel surgeries, such as bilateral knee replacement, however in these cases prior approval by the sponsor is required. In order to evaluate the activity of the product with respect to high-titer or high-responding inhibitors, at least 3 adult subjects with screening anti-hFVIII inhibitory antibody titers of ≥ 5 Bethesda units (BU) will be enrolled in the study.
Planned Duration of Subject Participation	The duration of subject participation depends on the nature of the invasive procedure: it will run from the signing of the informed consent until completion of the End of Study Visit (42 ± 7 days after last perioperative dose of BAX 802).

Primary Outcome Measure

The primary outcome measure is the proportion of all surgical, dental, or other invasive procedures with a "good" or "excellent" response as measured by GHEA score, which is composed of 3 individual ratings:

- GHEA1: Assessment of intraoperative (Day 0) hemostatic efficacy of BAX 802 performed by the operating surgeon at the end of surgery.
- GHEA2: Assessment of postoperative hemostatic efficacy of BAX 802 at postoperative Day 1 (approximately 24 hours [±6 hours] post-surgery) performed by the operating surgeon. (Note: If a patient is discharged < 24 hours following surgery, then the GHEA2 hemostatic efficacy assessment will require a return visit the following day.)
- GHEA3: Assessment of overall perioperative hemostatic efficacy of BAX 802 at the GHEA3 Visit (discharge or within 24 to 72 hours after the last perioperative treatment dose of BAX 802 if hospitalization is prolonged for reasons other than perioperative procedures [whichever is earlier]), performed by the Investigator, and where possible, also by the operating surgeon. Assessment by both is strongly recommended. In cases where there are differing assessments, the Investigator's assessment will be used.

The scores of each of the 3 individual ratings described above (GHEA1, GHEA2, and GHEA3), will be added together to form a GHEA score. Hemostatic efficacy success is defined as an "excellent" or "good "outcome for ≥ 70% of hemostatic efficacy assessments.

Secondary Outcome Measures

Efficacy

1. Intra- and post-operative blood loss compared to the estimated volume of expected average blood loss and expected maximum blood loss in a comparable healthy individual with similar demographic characteristics as predicted preoperatively by the Investigator/surgeon at the following time points:
   - Intraoperative, from start until the end of surgery
   - Postoperative Day 1, from end of surgery to approximately 24 hours ±6 hours after surgery
   - Overall perioperative at discharge or 24 to 72 hours after the last perioperative treatment dose of BAX 802 (whichever is earlier)
2. Proportion of major surgeries with good or excellent hemostatic outcome together with its 2-sided 95% confidence interval
3. Daily and total weight-adjusted administration of BAX 802 per subject
4. Amount of blood products (e.g. whole blood, red blood cells, platelets and plasma) transfused

Safety

1. Development of, and changes to, the titer of inhibitory and binding antibodies immunoglobulin G (IgG) and immunoglobulin M (IgM) to pFVIII
2. Development of, and changes to, the titer of inhibitory and binding antibodies (IgG and IgM) to hFVIII
3. Development of binding antibodies to BHK proteins
4. Occurrence of thrombo-embolic events
5. Incidence of severe allergic reactions (e.g., anaphylaxis)
6. Incidence of other IP-related AEs
7. Incidence of clinically significant changes in vital signs and routine laboratory parameters (hematology, clinical chemistry)

Exploratory Outcomes Measures

[redacted]

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form:** Injectable reconstituted solution of BAX 802, rpFVIII from which the B domain has been deleted. **Dosage frequency:** Loading dose, followed by subsequent individualized dosing. **Mode of Administration:** Intravenous bolus infusion (to the cubital vein is the recommended anatomical site of administration).
SUBJECT SELECTION	
Targeted Accrual	Enroll approximately 12 evaluable subjects (2 of which will be adolescents ≥ 12 to < 18 years old) for approximately 12 procedures.
Number of Groups/Arms/Cohorts	Single-arm

Inclusion Criteria

1. Subject requires a major or minor elective surgical, dental or other invasive procedure
2. Subject is male and ≥ 12 to ≤ 75 years old at the time of screening
3. Subject has provided signed informed consent (and assent for adolescent subjects, as applicable) in accordance with local regulatory requirements
4. Subject has severe (FVIII level < 1%) or moderately severe (FVIII level ≤ 2%) CHA with inhibitors to human FVIII (hFVIII), of ≥ 0.6 BU, as tested at screening at the central laboratory
5. Subject is not currently receiving or has recently received (< 30 days) immune tolerance induction (ITI) therapy
6. Subject has a Karnofsky performance score of ≥ 60 at screening
7. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm^3 at screening
8. Subject is hepatitis C virus negative (HCV-) by antibody or polymerase chain reaction (PCR) testing; or HCV+ with chronic stable hepatitis disease. Positive serologies will be confirmed by PCR testing.
9. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

1. The subject requires emergency surgery
2. Severe chronic liver dysfunction or disease (e.g., ≥ 5 × upper limit of normal [ULN] alanine aminotransferase [ALT], as confirmed by central laboratory at screening or a documented prothrombin time/international normalized ratio [PT/INR] > 1.5)
3. Clinically symptomatic renal disease (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening
4. Anti-porcine FVIII (pFVIII) > 10 BU prior to surgery
5. Platelet count < 100,000/µL at screening
6. Subject has another active coagulation disorder, other than hemophilia A, as per the medical history
7. Planned use of α-interferon with or without ribavarin for HCV infected patients or planned use of a protease inhibitor for HIV-infected patients. Patients currently taking any of these medications for ≥ 30 days are eligible
8. Known hypersensitivity to rpFVIII, or hamster or murine proteins
9. Subject has an ongoing or recent (within 3 months of screening) thrombo-embolic disease, fibrinolysis or disseminated intravascular coagulation (DIC).
10. Subject has been exposed to an IP 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
11. Subject is unable to tolerate quantity of blood to be drawn for protocol procedures
12. Subject is a family member or employee of the Investigator

STATISTICAL ANALYSIS

Sample Size Calculation

The sample size of approximately 12 surgeries/procedures in 12 evaluable male subjects (at least 5 major surgeries/procedures in 5 evaluable subjects), as defined in the protocol, was chosen to provide sufficient evidence of safety and effectiveness for this indication and is not based on statistical considerations.

Evaluable subjects are defined as subjects who met all study entry criteria and who had at least 1 hemostatic efficacy assessment.

Planned Statistical Analysis

Analysis Sets

The safety analysis set (SAS) will be comprised of all subjects who received any amount of BAX 802. The full analysis set (FAS) will be comprised of all surgeries with at least 1 available hemostatic assessment. The per-protocol analysis set (PPAS) will be comprised of all surgeries with evaluable ratings for all 3 perioperative hemostatic efficacy assessments, whose subjects met all study entry criteria and had no major protocol violations that might impact hemostatic efficacy assessments.

Primary Outcome Measure

The primary efficacy measure will be the overall assessment of hemostatic efficacy assessed intraoperatively and postoperatively by the surgeon at postoperative Day 1 (postoperative period, i.e., from end of surgery to 24 ±6 hours post-surgery) and perioperatively at 24 to 72 hours after the last perioperative treatment dose of BAX 802 is administered or discharge (whichever is earlier) by the surgeon and by the Investigator, and will be the sum of intraoperative, postoperative, and perioperative GHEA scores rated "excellent", "good", "fair" or "none".

Wherever possible (except for intraoperative assessment), bleeding should be assessed by both operating surgeon and Investigator. To achieve the hemostatic efficacy success criteria, the study needs to achieve a ≥ 70% rate of hemostatic efficacy assessments with an "excellent" or "good" outcome in at least 12 procedures.

Due to the possibility of a subject undergoing multiple surgeries, the statistical analysis of the primary outcome measure will be reported on the by-surgery level (i.e., not by the number of subjects). In cases where two or more surgical procedures are performed in the same intraoperative settings (under the same anesthesia, e.g., bilateral knee replacement) the surgery will be counted as one surgery. Blood loss assessment from those surgeries will be assessed as one. In the event that the subject is planning to have additional surgery in the future, the subject will need to complete the study and be re-screened again (if > 3 months from the screening) to ensure that they continue to meet the eligibility criteria.

Point estimates and corresponding 2-sided exact Clopper-Pearson confidence intervals (CIs) at the 95% confidence level will be calculated for the rate of hemostatic efficacy assessments with excellent/good outcome for descriptive purposes.

The proportion of all surgeries and of all major surgeries with hemostatic success will be reported along with exact 95% CIs. A treatment success will be defined as a rating of excellent or good.

The primary efficacy analysis will be based on the FAS population. As a supportive analysis, the same calculations will also be carried out on the PPAS population.

A sensitivity analysis based on the first surgery will be performed if more than 20% of subjects have multiple surgeries.

Any blood loss which is considered as unrelated bleeding (defined as any bleeding occurring at a different anatomical site other than the surgery site during the postoperative period) will not be taken into account for while making assessment of hemostatic efficacy for the primary efficacy measure.

Secondary Outcome Measures

Secondary hemostatic efficacy analysis:

Secondary outcome measures will be reported at the surgery level rather than the subject level. Descriptive statistics will be used to summarize the actual blood loss and transfusion requirements. The proportion of major surgeries with good or excellent hemostatic score together with its 2-sided 95% CI will be reported for descriptive purposes.

The summary of average daily and total weight-adjusted doses (average through postoperative 24 to 72 hours after last perioperative treatment dose of BAX 802 or discharge [whichever is earlier]) of BAX 802 per subject as well as the occurrence of bleeding episodes will be provided using descriptive statistics.

For unrelated bleeding episodes in the postoperative period, descriptive statistics will be used to summarize the overall hemostatic efficacy rating at 24 ±2 hours after initiation of treatment and at resolution of bleed (if not resolved within 24 hours). The secondary efficacy analysis will be performed on the FAS only. Separate descriptive summaries of average daily and total weight-adjusted doses required to treat unrelated bleeding episodes and will be provided.

Safety Analysis

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by presenting the number and proportion of subjects having any AE, having an AE in each system organ class, and having each individual AE as reported by preferred term. In the summaries, AEs will be counted only once per patient. If a patient reports the same AE more than once, it will be counted with its worst severity and closest relationship to the study product.

The number of subjects who experienced SAEs and the number of SAEs will be tabulated. In addition, the number of subjects who experienced AEs related to IP and the number of IP related AEs will be tabulated and subcategorized for thrombo-embolic events, inhibitory and total binding antibodies (IgG and IgM) to rpFVIII and hFVIII, and binding antibodies to BHK proteins.

An overview table for AEs will be provided, presenting the number of AEs, the number of subjects with AEs and the corresponding percent of subjects in total, and by seriousness and relationship to study treatment. An additional summary table will present the total number of (mild, moderate, severe) AEs by system organ class and preferred term with relationship to IP.

Summary statistics over time will be presented for the continuous laboratory parameters. Descriptive statistics of changes from baseline (prior to BAX 802 loading dose before the surgery) by study visits will also be presented.

A frequency table of results of categorical laboratory parameters will be produced. Furthermore, laboratory abnormalities will be analyzed by shift tables where each subject will be counted only once with the worst grade in the summary tables.

Vital signs assessments as well as the corresponding changes from baseline will be summarized descriptively at each scheduled or unscheduled assessment.

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AHA	acquired hemophilia A
AICC	anti-inhibitor coagulant complex
ALT	alanine aminotransferase
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
B19V	parvovirus B19
BHK	baby hamster kidney
BU	Bethesda units
CI	confidence interval
CHA	Congenital Hemophilia A
CRF	case report form
CTA	Clinical Trial Agreement
DIC	disseminated intravascular coagulation
DSMB	data safety monitoring board
EBL	estimated blood loss
EC	Ethics Committee
ELISA	enzyme-linked immunosorbent assay
EU	European Union
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FVIII	Factor VIII
GCP	Good Clinical Practice
GHEA	Global Hemostatic Efficacy Assessment
HAV	hepatitis A virus
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
HEV	hepatitis E virus
hFVIII	human factor VIII
HIV	human immunodeficiency virus

Abbreviation	Definition
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG	immunoglobulin G
IgM	immunoglobulin M
IP	investigational product
IPC	intermittent pneumatic compression
IRB	Institutional Review Board
ITI	immune tolerance induction
ITT	intent-to-treat
LMWH	low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
NMC	Non-medical complaint
OR	operating room
PCR	polymerase chain reaction
pFVIII	porcine factor VIII
PK	pharmacokinetics
PPAS	per protocol (analysis set)
PT/INR	prothrombin time/international normalized ratio
PV	plasma volume
rhFVIII	recombinant human factor VIII
rpFVIII	recombinant porcine factor VIII
RSI	Reference Safety Information
SAE	serious adverse event
SAER	serious adverse event report
SAP	statistical analysis plan
SAS	safety analysis set
SIC	subject identification code
SOC	standard of care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	thrombin generation assays
U	unit(s)
ULN	upper limit of normal
US	United States
US CFR	US Code of Federal Regulations
VIIa	activated factor VII
WFH	World Federation of Hemophilia

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

The investigational product (IP), BAX 802, is a recombinant form of porcine factor VIII (rpFVIII) from which the B domain has been deleted. Deletion of the B domain does not affect the safety or efficacy of this recombinant form of human factor VIII (rhFVIII) in the treatment of hemophilia A. BAX 802 (rpFVIII) is being developed for the perioperative management of hemostasis in subjects with congenital hemophilia A (CHA) with inhibitors to human factor VIII (hFVIII) undergoing surgical or other invasive procedures. This rpFVIII was approved by the United States Food and Drug Administration (FDA) in 2014 for the treatment of bleeding episodes in adults with acquired hemophilia A (AHA; non hemophilia subjects developing spontaneous autoantibody inhibitors to hFVIII) under the trade name OBIZUR®.

6.2 Clinical Condition/Indication

Congenital hemophilia A is a congenital bleeding disorder caused by a deficiency or complete absence of coagulation factor VIII (FVIII) [1] and is referred to as CHA in order to differentiate it from AHA, which is a rare autoimmune disease with different bleeding patterns caused by immunoglobulin G antibodies that bind to specific domains on the FVIII molecule, in a person with a negative personal or family history of a coagulopathy.[2]

Overall, CHA accounts for about 80% of hemophiliacs. It affects all ethnic populations and its prevalence varies among different countries, but is estimated at a rate of 3 to 20 cases per 100,000 population. The World Federation of Hemophilia (WFH) has estimated the total number of hemophilia cases at about 500,000 worldwide, of which one-third are diagnosed. The tendency to bleed in these subjects correlates with the plasma level of FVIII. This lifelong disorder has 3 clinical phenotypes (severe, moderate, and mild) that correlate with FVIII levels in plasma (< 1%, 1 to 5%, and 5 to 40%, respectively).[3]

Subjects with hemophilia A typically develop recurrent bleeding episodes. The most effective approach for treatment of acute bleeding episodes in subjects with hemophilia A is hFVIII replacement therapy.[4,5] However, a major complication in the treatment of subjects with hemophilia A is the development of neutralizing antibodies (inhibitors) to hFVIII, which impair the efficacy of replacement therapy with hFVIII concentrates. Inhibitor development occurs more frequently among patients with severe or moderately severe hemophilia, and approximately 30% of patients with severe CHA develop inhibitors. In CHA patients with high-responding inhibitors, standard replacement

therapy with FVIII concentrates is usually ineffective, resulting in poor control of hemorrhagic episodes. This, in turn, increases the risk of morbidity, mortality, orthopedic complications and disability, as well as reduced quality of life, compared with patients without inhibitors.[6] Patients with CHA with inhibitors are also at risk of perioperative bleeding complications, since replacement of the missing coagulation factor is ineffective, presenting a therapeutic challenge in elective or emergency surgery.[7]

Currently Available Treatments and Unmet Medical Need

In CHA patients with transient, low-responding, and/or low-titers (< 5 Bethesda units [BU]/mL) inhibitors, increased doses of FVIII may be sufficient to overcome the inhibitor and provide hemostasis. In CHA patients with high-responding inhibitors (> 5 BU/mL), standard replacement therapy with FVIII concentrates is usually ineffective, resulting in poor control of hemorrhagic episodes.

Alternative therapies are required for subjects with inhibitors who no longer respond to hFVIII replacement therapy. Recombinant activated factor VII (rFVIIa, NovoSeven®) and FEIBA (FVIII inhibitor bypassing activity; anti-inhibitor coagulant complex [AICC]) bypass the normal coagulation cascade and hence the FVIII inhibitors, and are therefore referred to as bypassing agents. Although these agents are able to manage bleeding in the presence of inhibitors, they do not attempt to restore the normal pathways of hemostasis, but instead boost thrombin generation despite a lack of platelet-surface FVIIIa–FIXa ('tenase') activity.[6] The measurement of levels of factor VIIa in the subject's plasma cannot be used as a clinically relevant surrogate marker and does not correlate with clinical outcome. Without an adequate biomarker, the dosage and treatment schedule cannot be clearly defined.[8] In addition, the response to rFVIIa treatment may be inconsistent both from subject to subject and between different bleeds in the same subject. Because FEIBA is a human plasma fraction containing several coagulation factors, it has the potential to transmit human pathogens and may also cause thromboembolic events. Since the plasma fraction also contains hFVIII, it has been associated with a rise in hFVIII antibodies in approximately 20% of subjects.[9] Moreover, as with rFVIIa, there is no validated biomarker that correlates with the clinical outcome with FEIBA treatment, although both thrombin generation assays (TGA) and whole blood viscoelastic assays have been evaluated for this purpose with some success.[10]

The ultimate goal of treatment for these patients is eradication of the inhibitor through immune tolerance induction (ITI), which involves frequent and long-term administration of factor concentrates in an attempt to build tolerance in the immune system to FVIII or factor IX, and thus restore responsiveness to factor replacement therapy. However, ITI fails in approximately 30% of inhibitor patients with CHA.[6]

There is therefore a clinical need for an effective hemostatic agent for use in subjects with CHA who have inhibitors to hFVIII, and which allows monitoring of hemostatic efficacy based upon measurement of plasma FVIII activity levels, thus facilitating early determination of clinical benefit and the patient's clinical status.

6.3 Population to be Studied

The study population will comprise of at least 12 procedures in 12 evaluable male subjects with CHA with inhibitors to hFVIII undergoing major or minor elective surgical, dental, or other invasive procedures (of which no more than 20% can be dental or other non-operative invasive procedures). Of 12 evaluable subjects, at least 2 will be adolescents (≥ 12 to < 18 years old), and in total there will be at least 5 major surgeries in 5 evaluable subjects. Subjects will be considered to be eligible provided that they satisfy all of the inclusion criteria listed in Section 9.1 and none of the exclusion criteria listed in Section 9.2. In order to evaluate the activity of the product with respect to high-titer or high-responding inhibitors to hFVIII, at least 3 adult subjects with screening anti-hFVIII inhibitor titers of ≥ 5 BU will be enrolled in the study.

6.4 Findings from Nonclinical and Clinical Studies

6.4.1 Finding from Nonclinical Studies

Nonclinical studies were performed with rpFVIII to demonstrate hemostatic activity in 2 animal models of hemophilia A (mice and dogs), local and systemic tolerance in a range of doses in single or repeat dose toxicology studies in monkeys, pharmacokinetics (PK) in dogs and monkeys, and immunogenicity in mice and monkeys.

Compatibility with the usual injection materials (needles, plastic syringes, and butterfly infusion needles with tubing) has been demonstrated. Studies in monkeys demonstrated the tolerability of repeated single daily injections of rpFVIII at doses up to 1000 U/kg, with injections at each dose level given once daily for 7 days. In 2 animal models of hemophilia A (mice and dogs), the hemostatic activity of rpFVIII was studied in comparison with Hyate:C. The rpFVIII was found to be efficacious in a dose-related fashion in controlling the bleeding associated with a standardized hemorrhagic insult. No animal studied was observed to have had an acute reaction to the injection of rpFVIII.

6.4.2 Findings from Clinical Studies

The safety and efficacy of rpFVIII was explored in 4 clinical trials prior to marketing approval:

- OBI-1-101 (N=9): a Phase 1, multicenter, randomized, double-blinded, double-dummy, parallel-group, comparison of the safety, tolerance, and PK study of rpFVIII versus Hyate:C was conducted.[11]
- OBI-1-201 (N=9): a Phase 2, prospective, open-label, non-comparative study was conducted to assess the hemostatic activity of rpFVIII. Eligible subjects had a clinical diagnosis of hemophilia A with inhibitors to hFVIII, an anti-pFVIII inhibitor antibody titer < 20 BU at screening, and an uncomplicated joint or soft tissue bleed, or other non-life threatening and non-limb threatening bleeding episode.[12]
- OBI-1-301 (N=29): a multicenter, open-label, single-cohort, prospective, Phase 2/3 study of rpFVIII in subjects with acquired hemophilia to determine the hemostatic efficacy and safety of rpFVIII in the control of serious bleeding episodes.[13]
- OBI-1-302 (terminated at N=1): a prospective, non-randomized, open-label study designed to assess treatment of serious bleeding episodes with rpFVIII in subjects with CHA who had developed anti-hFVIII inhibitors; this study was terminated by the sponsor after 1 subject was treated for administrative reasons, not due to safety or lack of efficacy concerns.

In all clinical studies, rpFVIII was generally well tolerated. There were no drug-related AEs reported in subjects who received rpFVIII in the Phase 1 study. One subject in the Phase 2 study (OBI-1-201) experienced pruritus (that resolved with diphenhydramine) that was possibly related to study drug. This AE occurred during the first bleeding episode, but the subject did not have a reaction during a second rpFVIII treated bleeding episode. In the Phase 1 and Phase 2 studies, no AEs led to treatment interruption, discontinuation from the study, or death. Vital signs, laboratory values, medical history and physical examination findings were within normal parameters for both studies and raised no safety concerns.

In the Phase 2 study (OBI-1-201), the intent-to-treat (ITT) population consisted of 9 male subjects with CHA and with an inhibitor antibody to hFVIII. Six of the subjects (67%) were black and 3 subjects (33%) were Caucasian. The mean age of the subject population was 23.7 years (range: 14 to 34). The primary efficacy objective of the study was to evaluate the hemostatic efficacy of rpFVIII in the treatment of non-life/non-limb threatening bleeds in subjects with CHA and inhibitors.

A total of 25 bleeds in 9 subjects were treated with rpFVIII and all bleeds were successfully controlled with 8 or less injections of rpFVIII. The median number of rpFVIII injections administered per bleeding episode was 1.0 (range: 1 to 8) and the median time from bleeding onset to treatment was 5.67 hours (range: 1.5 to 20.0). Across all bleeding episodes the median total dose of rpFVIII per bleeding episode was 224.1 U/kg (range: 50.0 to 1066.4). The median initial Treatment Dose (including the loading dose if applicable), was 159 U/kg (range: 50 to 576) and resulted in a median increase of FVIII plasma level of 16 % with the 1-stage clotting assay (range: 0.5% to 427%) and a median increase of 17% with the chromogenic assay (range: 0% to 248%). Twenty of the 25 (80%) bleeds were controlled within 6 hours having been administered 1 Treatment Dose of rpFVIII. For those 20 bleeds controlled with 1 Treatment Dose (including the loading dose if applicable), the median dose was 200.8 U/kg. The rpFVIII was well tolerated and of the reported AEs (n=61) only 18 AEs were considered treatment emergent. Two subjects reported an AE that was possibly related to study drug. One AE of itching/pruritus during the first bleeding episode but without reaction during a second rpFVIII treated bleeding episode. The second AE was a report of increased ALT and aspartate aminotransferase (AST), possibly associated with a confirmed hepatitis C infection, while it was uncertain whether the corresponding blood sample was taken before or after rpFVIII administration. Three subjects suffered treatment emergent SAEs but none were considered related to study drug. No reported AE led to treatment interruption, discontinuation from the study or death. Eight out of 9 (8/9, 89%) subjects developed anti-pFVIII antibodies following exposure to rpFVIII. In subjects who received repeated rpFVIII treatment, higher anti-pFVIII titers did not affect efficacy or safety and no increase in AEs or bleeding episodes were reported in the subjects with the highest titers. Regardless of the observed anti-pFVIII titers at pre-treatment or the obtained FVIII recovery values after treatment initiation, all bleeding episodes were successfully controlled. Analyses of baby hamster kidney (BHK; host cell line) antibody levels indicated that no subjects produced detectable levels of antibodies against BHK.

In the prospective, open-label trial (OBI-1-301), the efficacy of rpFVIII for the treatment of serious bleeding episodes in subjects with AHA was investigated. The trial was conducted in 18 Caucasian, 6 African-American, and 5 Asian subjects diagnosed with AHA, having auto-immune inhibitory antibodies to hFVIII, and experiencing serious bleeding episodes that required hospitalization. Subjects with a prior history of bleeding disorders other than AHA, anti-pFVIII antibody titer > 20 BU, or in whom the bleeding episode was judged likely to resolve on its own, were excluded. One subject was considered evaluable at study entry; however, it was later determined that this subject did not have AHA, leaving 28 subjects evaluable for efficacy. Of the 28 subjects evaluable for efficacy, all subjects had a positive response to treatment for the initial bleeding

episodes at 24 hours after dosing. A positive response was observed in 95% (19/20) of subjects evaluated at 8 hours and 100% (18/18) at 16 hours. In addition to response to treatment, the overall treatment success was determined by the Investigator based on his/her ability to discontinue or reduce the dose and/or dosing frequency of rpFVIII. A total of 24/28 subjects (86%) had successful treatment of the initial bleeding episode. Of those subjects treated with rpFVIII as first-line therapy, defined as no immediate previous use of anti-hemorrhagic agents prior to the first rpFVIII treatment, 16/17 subjects (94%) had eventual treatment success reported. Eleven subjects were reported to have received anti-hemorrhagics (eg, rFVIIa, activated prothrombin-complex concentrate, and tranexamic acid) prior to first treatment with rpFVIII. Of these 11 subjects, 8 had eventual successful treatment (73%). No related serious adverse reactions occurred. Non-serious AEs related to treatment were noted and assessed by the Investigator in 6/29 subjects (20.7%). One subject had mild tachycardia, hypotension and constipation. One subject had 2 instances of mild peripherally inserted central catheter (PICC) line occlusion. One subject had a mild hypofibrogenemia and 1 subject had moderate mental status changes. All of these adverse effects completely resolved. Two subjects developed anti- pFVIII inhibitors after infusion of study drug (range 8 to 51 BU) and were discontinued from treatment; however both subjects had a positive response to treatment at the 24-hour primary endpoint assessment. An investigation was conducted by the sponsor and, in summary, the 2 incidences of anti-pFVIII inhibitors were considered related to rpFVIII treatment, while the other non-serious treatment-related adverse events were considered as unlikely to be related to rpFVIII. Anti-pFVIII inhibitors were detected prior to infusion in 10/29 patients (range 0.8 to 29 BU). All of these subjects had a positive response at 24 hours post-rpFVIII first infusion. No anti-BHK antibodies were observed in any of the 29 treated subjects.

At the time of OBIZUR® marketing approval, the clinical trial data indicated that rpFVIII was well tolerated and had demonstrated effectiveness in the control of bleeding in study subjects. Cumulatively (patient exposure from 01 Oct 2014 through 31 Oct 2016), approximately 16,424,000 units (U) of OBIZUR® were sold worldwide. Median (range) treatment dose per bleeding episode was 94,500 (35,256 to 182,700), and the estimated number of patient-years worldwide to OBIZUR® was approximately 347.6 (179.8 to 931.6). As of 11 Nov 2016, there have been 20 post-marketing serious case reports with 36 AEs. No adverse reactions other than those observed in clinical trials have been observed in the post marketing setting. The reports were consistent with the known safety profile of OBIZUR®.[i]

[i] Obizur Periodic Safety Update Report/Periodic Benefit-Risk Evaluation Report (PSUR/PBRER), reporting interval 12 MAY 2016 to 11 NOV 2016.

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

Porcine FVIII (Hyate:C), derived from porcine plasma, had been used successfully starting in the 1980s to achieve hemostasis in the presence of anti-hFVIII inhibitors, as the antibodies generally have low immunological cross-reactivity with pFVIII.[14] However, the number of hemophilia A subjects who were appropriate candidates to receive Hyate:C was limited by the degree to which their anti-hFVIII antibodies cross-reacted with pFVIII and the presence of any anti-pFVIII inhibitors. While a median inhibitor cross-reactivity observed to porcine VIIIC was only 15%, an absent, intermediate, or brisk specific anti-porcine anamnestic response was observed in 29%, 40%, and 31% of patients, respectively.[15] The commercial production of Hyate:C was discontinued in 2005 due to problems with sourcing suitable porcine plasma, but not due to any safety or efficacy concerns.

BAX 802 is a B-domain deleted rpFVIII glycoprotein which is being developed for the perioperative management of hemostasis in subjects with CHA with FVIII inhibitors undergoing surgical or other invasive procedures. B-domain deleted rpFVIII glycoprotein has been extensively studied. BAX 802 (as marketed OBIZUR®) is not currently indicated for the treatment of CHA.[16]

OBIZUR® was approved based on the safety and efficacy data from 28 subjects with AHA treated with B-domain deleted rpFVIII glycoprotein in the Phase 2/3 open-label clinical study OBI-1-301. The safety, hemostatic activity, and PK profile of B-domain deleted rpFVIII glycoprotein was also supported by results of an open-label Phase 2 study in patients with CHA with inhibitors (Clinical Study Report OBI-1-201), and a randomized Phase 1 study comparing B-domain deleted rpFVIII glycoprotein with a plasma-derived pFVIII (CSR OBI-1-101).

The data supported the use of B-domain deleted rpFVIII glycoprotein to treat serious bleeding episodes in AHA patients (Section 6.4.2). It was demonstrated that B-domain deleted rpFVIII glycoprotein provides benefit to AHA patients who are unresponsive to alternative agents with an improved dosing algorithm. It was possible to monitor hemostatic efficacy based upon measurement of plasma FVIII activity levels, thus facilitating early determination of clinical benefit and the patient's clinical status. An additional benefit to the patient was that it was possible to adjust the dose based on the FVIII levels rather than follow fixed dosing, ensuring that adequate doses were administered to achieve hemostasis.

The most frequently reported adverse reaction in patients with AHA was the development of inhibitors to pFVIII.[16]

Overall, efficacy and safety clinical data for OBIZUR supported a favorable benefit/risk determination for the proposed indication of treatment of bleeding episodes in adults with AHA.

These data support the investigation of efficacy and safety of BAX 802 in subjects with CHA with inhibitors undergoing surgical or other invasive procedures.

6.6 Compliance Statement

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

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is to evaluate the efficacy and safety of BAX 802 in males with CHA with inhibitors who are undergoing major or minor elective surgical, dental, or other invasive procedures.

7.2 Primary Objective

The primary objective of the study is to evaluate the perioperative hemostatic efficacy of BAX 802 in male subjects with CHA with inhibitors to hFVIII undergoing major or minor elective surgical, dental, or other invasive procedures as determined by the Global Hemostatic Efficacy Assessment (GHEA) score.

7.3 Secondary Objectives

The secondary objectives of the study are:

1. To determine the safety of BAX 802 used in the perioperative setting by assessing:
    - The development of and change in titer of anti-pFVIII and anti-hFVIII antibodies (binding and neutralizing), and development of binding antibodies to BHK proteins
    - The occurrence of thrombo-embolic events and/or allergic reactions to BAX 802
    - The occurrence of AEs related to BAX 802
    - The occurrence of clinically significant changes in vital signs and routine laboratory parameters related to BAX 802
2. To determine the intraoperative, postoperative, and overall perioperative blood loss, compared to the estimated volume of expected average and maximum blood loss in a comparable healthy individual as predicted preoperatively by the Investigator/surgeon
3. To determine the proportion of major surgeries with good or excellent hemostatic score
4. To determine the daily and total weight-adjusted administration of BAX 802 per subject

7.4 Exploratory Objectives

The exploratory objectives of the study are:

[redacted]

8. STUDY DESIGN

8.1 Brief Summary

This study is a Phase 3, prospective, single-arm, open-label, uncontrolled, multicenter study to evaluate the efficacy and safety of BAX 802 in at least 12 procedures in 12 evaluable male subjects ≥ 12 to ≤ 75 years old with CHA with inhibitors to hFVIII who are undergoing major and minor surgical, dental or other invasive procedures. At least 5 of the procedures must be major surgeries in 5 evaluable subjects, of which no more than 20% can be dental or other non-operative invasive procedures (see Section 8.2.1), and at least 3 adult subjects with screening anti-hFVIII titers of ≥ 5 BU for inhibitors to human FVIII will be enrolled in the study. At least 2 adolescents (≥ 12 to < 18 years old) will be enrolled in the study.

8.2 Overall Study Design

The dose and frequency of BAX 802 during the preoperative, intraoperative, and postoperative periods should follow a proposed substitution plan provided by the Investigator to the medical monitor prior to surgery and adjusted based on regular FVIII activity measurements (see Section 8.7.3.1). The regimen will depend on the type of surgery performed and the intensity of the hemostatic challenge.

Elective surgical procedures will prospectively be defined as major or minor by the Investigator/surgeon and agreed with the medical director/designee, based on the protocol guidance and definitions and in consideration of each subject's characteristics. Emergency surgeries are not in the scope of this study. Subjects may undergo more than 1 surgery or 2 parallel surgeries, such as bilateral knee replacement. For subjects undergoing multiple surgeries (other than parallel surgeries), the End of Study visit should be completed for the first surgery and then subject needs to be re-screened (Section 10.3) for the next surgery.

The study will be divided into 5 periods: Screening, Preoperative, Intraoperative, Postoperative, and End of study (Table 8). The study will be conducted at multiple sites in North America, Europe, and South Africa.

The overall study design is illustrated in Figure 2.

8.2.1 Types of Interventions

Elective surgeries and other invasive procedures will prospectively be defined by the Investigator/surgeon as major or minor based on the definitions and examples provided in Section 8.2.1.1 and Section 8.2.1.2, respectively, taking into consideration each individual patient's characteristics and agreement with the sponsor.

8.2.1.1 Major Surgeries

Major surgeries include surgeries that require moderate or deep sedation, general anesthesia, or major conduction blockade for patient comfort. This generally refers to major orthopedic (e.g., joint replacement), major abdominal, intracranial, cardiovascular, spinal and any other surgery which has a significant risk of large volume blood loss (> 500 mL) or blood loss into a confined anatomical space. Extraction of at least 3 teeth or extraction of the third molar are generally considered as major. Examples include:

- bone fixation for fracture
- hip and knee replacement (arthroplasty)
- arthrodesis (joint fusion)
- open synovectomy
- osteotomy
- liver biopsy
- pseudotumor removal
- hardware removal (plates and intramedullary nails)

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

8.2.1.2 Minor Surgeries

Minor surgeries include surgeries that can be safely and comfortably performed on a patient who has received local or topical anesthesia, without more than minimal preoperative medication or minimal preoperative medication or minimal intraoperative sedation. The estimated total blood loss should be < 500 mL and the likelihood of complications requiring hospitalization or prolonged hospitalization should be remote. It refers to interventions such as removal of skin lesions, arthroscopy, minor dental procedures or dental extractions. Examples include:

- removal of skin lesions
- minor dental procedures or dental extractions (except extraction of 3 or more teeth or third molar extraction)
- placement and/or removal of central venous catheters
- synoviorthesis and arthrocentesis

- arthroscopy
- 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

8.2.2 Dose Selection Rationale

Background

This is a Phase 3, multicenter, single-arm, open-label study of the efficacy and safety of B-domain deleted rpFVIII (BAX 802) in the perioperative management of hemostasis in subjects with CHA who have inhibitors and are undergoing surgical or other invasive procedures. The rpFVIII temporarily replaces the inhibited FVIII that is needed for effective hemostasis in CHA patients who have developed inhibitors to hFVIII. The principle of using pFVIII is based on its low cross-reactivity with anti-hFVIII antibodies due to sequence variations between human and pFVIII in the A2 and C2 domains, the main targets of FVIII inhibitors. The rpFVIII concentrate is predicted to have an advantage over human-derived FVIII in CHA patients who have inhibitors since previous studies demonstrated that the antibodies have a median of only 15% cross-reactivity with plasma-derived pFVIII.[17]

Regulatory approval for rpFVIII for the treatment of bleeding episodes in adults with AHA was received for OBIZUR®; per the product label, the initial dose of OBIZUR® is 200 U/kg, with subsequent dosing dependent on the location and severity of bleeding episode, target FVIII levels, and the patient's clinical condition.[16]

Influence of Anti-pFVIII Inhibitor Titer on the Loading Dose

Anti-pFVIII inhibitors are neutralizing antibodies against pFVIII that neutralize the pFVIII, and thereby reduce its hemostasis effect. Anti-pFVIII inhibitors can be quantified in plasma by the Bethesda assay, which measures the ability of the patient's plasma to neutralize exogenous pFVIII when incubated together.

The amount of BAX 802 required to neutralize the anti-pFVIII activity is factored in. A BU is defined as the amount of anti-pFVIII inhibitor in a plasma sample which will neutralize 50% of 1 unit of BAX 802 in normal plasma after 2 hour incubation at 37°C.

Only the inhibitor that is distributed in the plasma volume (PV) is initially available to neutralize the infused FVIII; PV is calculated using the following formula:

$$PV = \text{Blood Volume} \times (1 - [\text{hematocrit}\{HCT\}\%/100])$$

Normal blood volume is approximately 80 mL/kg for adults.

Therefore, $PV = 80 \times (1 - [HCT\%/100])$.

One BU of anti-pFVIII inhibitor will neutralize 50% of 1 unit of BAX 802; therefore, it is assumed that 0.5 U FVIII will be required for each 1 BU of inhibitor. The amount of BAX 802 required to neutralize the anti-pFVIII activity can be estimated using the following:

$$\text{Body weight} \times 80(1 - [HCT\%/100]) \times 0.5 \times \text{anti-pFVIII inhibitor titer (BU/mL)} = \text{body weight} \times 40(1-[HCT\%/100]) \times \text{anti-pFVIII inhibitor titer (BU/mL)}.$$

Proposed Dosing Regimen of BAX 802 in Study BAX 802 Surgery

The dosing scheme to be used in Study BAX 802 Surgery is presented in Section 8.7.3.3.

The loading dose of BAX 802 (in U) for a CHA subject with inhibitors undergoing major surgery is calculated using the following formula:

$$[80 \times \text{body weight (kg)}]\ U + [\text{body weight (kg)} \times 40(1-[HCT\%/100]) \times \text{anti-pFVIII inhibitor titer (BU/mL)}]\ U$$

For example, for a 70 kg subject undergoing major surgery and having HCT 45% and anti-pFVIII inhibitor titer 3 BU/mL, the loading dose of BAX 802 will is calculated as follows:

$$[80\ (70)]\ U + [70 \times 40(1-[45/100]) \times 3]\ U = 10{,}220\ U$$

This dosing scheme should reasonably predict the loading dose before surgery that will provide sufficient FVIII levels needed for effective hemostasis.

Subsequent doses, dosing frequency, and duration of treatment will be based on clinical judgment and measured FVIII levels achieved, and will require empirically based adjustments until hemostasis is achieved (Table 5).

This dosing algorithm is essentially equivalent to that proposed by Kasper (2004) when using FVIII in the treatment of patients with low titer inhibitors.[18]

8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study will be approximately 28 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject, last visit). The recruitment period is expected to be approximately 24 months. A subject is considered enrolled if he has signed the Informed Consent Form.

The duration of subject participation depends on the nature of the invasive procedure: it will run from the signing of the informed consent until completion of the End of Study Visit 42 ± 7 days after last perioperative dose of BAX 802 (end of surgery = Day 0), unless prematurely discontinued. Study completion is defined by the End of Study Visit.

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

The primary outcome measure is the proportion of all surgical, dental, or other invasive procedures with a "good" or "excellent" response as measured by GHEA score (Table 1), which is composed of 3 individual ratings:

- GHEA1: Assessment of intraoperative (Day 0) hemostatic efficacy of BAX 802 performed by the operating surgeon (see Table 2) at the end of surgery
- GHEA2: Assessment of postoperative hemostatic efficacy of BAX 802 at postoperative Day 1 (approximately 24 hours [± 6 hours] post-surgery) performed by the operating surgeon. (Note: If a patient is discharged < 24 hours following surgery, then the GHEA2 hemostatic efficacy assessment will require a return visit the following day) (see Table 3)
- GHEA3: Assessment of overall perioperative hemostatic efficacy of BAX 802 at the GHEA3 Visit (discharge or within 24 to 72 hours after the last perioperative treatment dose of BAX 802 [whichever is earlier]), performed by the Investigator, and where possible, also by the operating surgeon. Assessment by both is strongly recommended. In cases where there are differing assessments, the Investigator's assessment will be used (see Table 4).

(Note: In cases such as minor surgeries/procedures, there might be a possibility that the subject is discharged < 24 hours following the surgery/procedure but continues receiving BAX 802 in hospital (e.g., day hospital) setting. In these cases, the GHEA2 hemostatic efficacy assessment should be performed the following day. Also, the GHEA3 Visit should be performed within 24 to 72 hours after the last perioperative treatment dose of BAX 802. Both GHEA2 and GHEA3 assessments can be performed on the day after the surgery/procedure if the subject does not need any further BAX 802 administration for perioperative management.)

Prior to the surgery, the surgeon/Investigator will predict the estimated volume (in mL) of the expected 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 and from completion of the procedure until approximately 24 hours post-surgery and for the overall perioperative period (see Section 11.2.1).

The scores of each of the 3 individual ratings (GHEA1, GHEA2, and GHEA3) described above, will be added together to form a GHEA score according to Table 1. For a GHEA score of 7 to be rated "excellent" no individual assessment score should be less than 2 (i.e., one individual assessment score must be 3 and the other two individual assessment scores must be 2). The only other option to achieve a GHEA score of 7 is for two individual assessment scores of 3 and one individual assessment score of 1. Although this GHEA score will not qualify for a rating of "excellent," the GHEA score will satisfy the definition of "good," (with no individual assessment score less than 1). All possible combinations of the individual assessment scores and their related ratings are provided in Supplement 20.5.

For surgeries with up to 2 missing hemostatic assessments that did not necessitate rescue therapies, the rating of "fair" will be imputed for these missing data. These surgeries will be included in the full analysis set (FAS). The assessment of primary outcome measure (GHEA score) should only account for the blood loss related to the surgery and exclude any blood loss which is considered as unrelated bleeding (defined as any bleeding occurring at a different anatomical site than the surgery site during the postoperative period, see Section 11.2.5).

Table 1
Global Hemostatic Efficacy Assessment (GHEA)

Assessment	GHEA Score
Excellent	7[a] to 9 (with no category scored < 2)
Good	5 to 7[a] (with no category scored < 1)
Fair	3 to 4 (with no category scored < 1)
None	0 to 2 (or at least one category scored 0)

[a] For a GHEA score of 7 to be rated "excellent" (with no individual assessment scores less than 2), at least 1 individual assessment score must be 3 and the other 2 individual assessment scores must be at least 2; otherwise a score of 7 is rated "good".

Table 2
Intraoperative Efficacy Assessment Scale (GHEA1)

	At the end of surgery, the operating surgeon will assess the intraoperative hemostatic efficacy	
Rating	**Criteria**	**Score**
Excellent	Intraoperative blood loss was less than or equal to that expected for the type of procedure performed in a non-hemophilic population (≤ 100%)	3
Good	Intraoperative blood loss was up to 50% more than expected for the type of procedure performed in a non-hemophilic population (101 to 150%)	2
Fair	Intraoperative blood loss was more than 50% of that expected for the type of procedure performed in a non-hemophilic population (> 150%)	1
None	Uncontrolled hemorrhage that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy or other FVIII products	0

Table 3
Postoperative Efficacy Assessment Scale (GHEA2) (Postoperative Day 1)

	On postoperative Day 1 (24 ± 6 hours post-surgery), the operating surgeon will assess the postoperative hemostatic efficacy	
Rating	**Criteria**	**Score**
Excellent	Postoperative blood loss was less than or equal to (≤ 100%) that expected for the type of procedure performed in a non-hemophilic population	3
Good	Postoperative blood loss was up to 50% more (101% to 150%) than expected for the type of procedure performed in a non-hemophilic population	2
Fair	Postoperative blood loss was more than 50% (> 150%) of that expected for the type of procedure performed in a non-hemophilic population	1
None	Significant postoperative bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy or other FVIII products	0

Table 4
Overall Perioperative Efficacy Assessment Scale (GHEA3) (at Discharge or Within 24 to 72 hours after the last perioperative treatment dose of BAX 802 [whichever is earlier])

	At discharge or within 24 to 72 hours after the last perioperative treatment dose of BAX 802 (whichever is earlier), the postoperative efficacy assessment will be performed by the Investigator, and where possible, also by the operating surgeon	
Rating	**Criteria**	**Score**
Excellent	Overall perioperative blood loss was less than or equal to (≤ 100%) that expected for the type of procedure performed in a non-hemophilic population, Required blood components for transfusions were less than or similar to that expected in non-hemophilic population	3
Good	Overall perioperative blood loss was up to 50% more (101% to 150%) than expected for the type of procedure performed in a non-hemophilic population Required blood components for transfusions were less than or similar to that expected in non-hemophilic population	2
Fair	Overall perioperative blood loss was more than 50% of that expected for the type of procedure performed in a non-hemophilic population (> 150%) Required blood components transfusions were greater than that expected in non-hemophilic population	1
None	Significant overall perioperative bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy or other FVIII products Required blood components for transfusions were substantially greater than that expected in non-hemophilic population	0

Hemostatic efficacy success is defined as "excellent" or "good "outcome for ≥ 70% of hemostatic efficacy assessments.

8.4.2 Secondary Outcome Measures

8.4.2.1 Efficacy

1. Intra- and post-operative blood loss compared to the estimated volume of expected average blood loss and expected maximum blood loss in a comparable healthy individual with similar demographic characteristics as predicted preoperatively by the Investigator/surgeon at the following time points:
   - Intraoperative, from start until the end of surgery
   - Postoperative Day 1, from end of surgery to approximately 24 hours (± 6 hours) after surgery
   - Overall perioperative at discharge or 24 to 72 hours after the last perioperative treatment dose of BAX 802 (whichever is earlier)
2. Proportion of major surgeries with good or excellent hemostatic score
3. Daily and total weight-adjusted administration of BAX 802 per subject
4. Amount of blood products (e.g., whole blood, red blood cells, platelets and plasma) transfused

8.4.2.2 Safety

1. Development of, and changes to, the titer of inhibitory and binding antibodies (IgG and IgM) to pFVIII
2. Development of, and changes to, the titer of inhibitory and binding antibodies (IgG and IgM) to hFVIII
3. Development of binding antibodies to BHK proteins
4. Occurrence of thrombo-embolic events
5. Incidence of severe allergic reactions (e.g., anaphylaxis)
6. Incidence of other IP-related AEs
7. Incidence of clinically significant changes in vital signs and routine laboratory parameters (hematology, clinical chemistry)

8.4.3 Exploratory Outcome Measures

[redacted]

8.5 Randomization and Blinding

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

8.6 Study Stopping Rules

The study will be halted (enrollment stopped), pending further review by the external data safety monitoring board (DSMB) and sponsor, if 1 or more of the following criteria are met:

1. Two or more subjects develop a severe anaphylactic reaction or any other serious adverse event (SAE) related to BAX 802 that would not be expected
2. The occurrence of Suspected Unexpected Serious Adverse Reaction (SUSAR)
3. Other AEs that are deemed to pose unacceptable risks to subjects.

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

1. The sponsor decides to terminate the study based upon DSMB recommendation or its own assessment of safety
2. The sponsor decides to terminate the study at any time for administrative reasons.

8.7 Investigational Product(s)

The IP, BAX 802, is a recombinant purified form of rpFVIII from which the B domain has been deleted and replaced with a 24 amino acid linker. Recombinant pFVIII (BAX802) is expressed as a glycoprotein by a genetically engineered BHK cell line. The molecular weight of rpFVIII is approximately 175 kDa (based on its 1448 amino acid sequence) and has 86% pair-wise sequence homology with hFVIII.

BAX 802 will be supplied as white lyophilized powder in 3 mL glass vials containing nominally 500 units per vial for reconstitution with 1.0 mL sterile water for injection.

8.7.1 Packaging, Labeling, and Storage

BAX 802 will be supplied in a lyophilized form. For specific instructions for reconstitution, please refer to the Pharmacy Manual. A sufficient quantity of BAX 802 will be supplied to each study site, as well as an acknowledgement of receipt form.

The core label texts for all packaging units will be translated or adjusted, to be in compliance with applicable regulatory requirements, national laws in force and in accordance with the local languages. Minimally each vial will bear a label with the following information:

- Sponsor name
- Study number
- Pharmaceutical dosage form
- Route of administration
- Name of IP and actual quantity of dose units
- Batch number
- Space on which to record the subject number
- The statement ‘For clinical trial use only’ or ‘Caution: new drug limited by Federal Law to investigational use’ or ‘To be used only by a qualified Investigator’, as appropriate
- Name, address and telephone number of the Sponsor, Contract Research Organization or Investigator, if appropriate
- Storage conditions
- Expiry or manufacturing date, as appropriate

The Investigator or designee will only dispense BAX 802 to subjects included in this study.

BAX 802 should be kept refrigerated at 2°C to 8°C (36°F to 46°F). The following precautions should be taken:

- Do not freeze
- Do not use if frozen, even if it has been thawed
- Do not use beyond the expiration date printed on the carton or vial
- Do not use after > 3 hours of reconstitution.

8.7.2 Reconstitution and Administration

The reconstitution procedures for BAX 802 are detailed in the Pharmacy Manual. Reconstituted BAX 802 should be kept and administered at room temperature and must be administered within 3 hours of reconstitution.

BAX 802 will be administered as an intravenous bolus infusion to the cubital vein per the dosing schema for major and minor surgeries (Table 5).

8.7.3 Description of Treatment

8.7.3.1 FVIII Maintenance Plan

Based on the category (minor or major) and type of surgery and prior to intervention, the Investigator should outline the expected FVIII maintenance plan with target peak and trough levels covering the surgical, dental or invasive procedure until expected wound healing. The FVIII maintenance plan should be communicated to the medical director/designee to ensure that the recommendations regarding FVIII target levels as provided in the protocol are followed (see Table 5). Each FVIII maintenance plan for major surgeries requires prior approval of the medical director. The FVIII levels measured intra/postoperatively will be compared with the FVIII maintenance plan. Slight deviations from the predefined plan are allowed based on Investigators clinical judgment and/or available laboratory FVIII data.

It is recommended that the turnaround time for FVIII activity results from the local laboratories are ≤ 2 hours so that dosing decisions could be made and subjects are dosed adequately.

8.7.3.2 Perioperative Dosing

Adjustments to the dose and frequency of BAX 802 dosing during the intra- and postoperative period should follow the maintenance plan provided by the Investigator prior to surgery. Adjustments must be based on regular FVIII activity measurements determined at pre- and post-dosing of BAX 802 and will depend on the type of the surgery performed and the intensity of the hemostatic challenge.

8.7.3.3 Dosing Schedule and Requirements

8.7.3.3.1 General

As described in Section 8.2.2, the loading dose will be calculated according to the following formula:

Loading dose of BAX 802 (administered approximately 1 to 2 hours prior to the surgery)**:**

- **Major Surgery:**
  [80 × body weight (kg)] U + [body weight (kg) × 40(1-[HCT%/100]) x anti-pFVIII inhibitor titer (BU/mL)] U
- **Minor Surgery:**
  [50 × body weight (kg)] U + body weight (kg) × 40(1-[HCT%/100]) × anti-pFVIII inhibitor titer (BU/mL)] U

For example, for a 70 kg subject undergoing major surgery and having HCT 45% and anti-pFVIII inhibitor titer 3 BU/mL, the loading dose of BAX 802 will be calculated as follows:

$$80\ (70) + 70 \times 40(1-[45/100]) \times 3 = 10{,}220\ \text{U}$$

Subsequent doses, dosing frequency, and duration of treatment will be based on clinical judgment and measured FVIII levels, and will require empirically based adjustments until hemostasis is achieved based on the following calculation below (Table 5):

- **Required (subsequent) dose (U) =** [body weight (kg) × desired FVIII rise (U/dL or % of normal)]/1.2 (U/kg per U/dL).

Table 5
Dosing for Perioperative Management

Type of Surgery	Recommended FVIII Level (% of normal or U/dL)	Loading Dose (U)	Subsequent Dose (U)
Major (see Section 8.2.1.1)	**Prior to surgery:** ≥ 80% **Postoperative up to 72 hours (if not yet discharged and GHEA3 not yet performed):** ≥ 80% **Postoperative Day 4 – Day 7 (if not yet discharged and GHEA3 not yet performed):** ≥ 50% **After Postoperative Day 8 (if not yet discharged and GHEA3 not yet performed):** it is recommended that the FVIII levels do not fall below 30% (left to the discretion of the Investigator depending on the postoperative course)	[80 × body weight (kg)] U + [body weight (kg) × 40(1-[HCT%/100]) × anti-pFVIII inhibitor titer (BU/mL)[a]] U, administered approximately 1 to 2 hours prior to the surgery	Titrate subsequent doses to maintain recommended FVIII trough levels and individual clinical response using following formula: Required dose (U) = [body weight (kg) × desired FVIII rise (U/dL or % of normal)]/1.2 (U/kg per U/dL)
Minor (see Section 8.2.1.2)	**Prior to surgery:** ≥ 50% **Postoperative up to 72 hours (if not yet discharged and GHEA3 not yet performed):** ≥ 50% **After Postoperative Day 4 (if not yet discharged and GHEA3 not yet performed):** it is recommended that the FVIII levels do not fall below 30% (left to the discretion of the Investigator depending on the postoperative course)	[50 × body weight (kg)] U + [body weight (kg) × 40(1-[HCT%/100]) × anti-pFVIII inhibitor titer (BU/mL)[a]] U, administered approximately 1 to 2 hours prior to the surgery	

[a] Anti-pFVIII inhibitor titer and hematocrit information available from screening laboratory result will be used.

Note: It is recommended that the plasma levels of FVIII do not exceed 200% of normal.

If at any time during the study, a subject does not respond to BAX 802 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. In the event of unexplained, excessive bleeding, the subject will be treated by whatever means necessary until adequate hemostasis is achieved. If other rescue medications become necessary, the subject will subsequently be withdrawn from this BAX 802 surgery study and considered a treatment failure and assigned a GHEA score of 0 for remaining assessments (if any). Adverse events and the details of concomitant medication and blood product use coincident with the treatment of all unanticipated bleeding will be recorded. The use of adjunct antifibrinolytic therapy (such as tranexamic acid) is allowed if clinically indicated by the Investigator and/or according to the standard of care (SOC) of the subject's institution.

8.7.3.3.2 Preoperative and Loading Dose

The subject will receive a loading dose calculated according to the formula described in Section 8.7.3.3.1 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 to 120 minutes prior to surgery (prior to incision/intubation).

The recommended FVIII target level is ≥ 80% for major surgeries/procedures and ≥ 50% for minor surgeries/procedures.

It is recommended that the surgery starts after FVIII levels have achieved target levels. However, if FVIII activity post loading dose is close to the target level, a supplemental dose of BAX 802 should be administered without further delaying the surgery, based on Investigator's judgement. Close to the target for major and minor surgeries will be defined as levels of ≥ 70% for major and ≥ 40% for minor surgeries, respectively. This is 10% from the target, which is considered a normal assay variation.

If FVIII activity post loading dose is not close to the target level, a supplement dose of BAX 802 should be administered and surgery delayed until FVIII levels have achieved target levels or are in close range.

Subjects will receive subsequent doses of BAX 802 in order to achieve the FVIII target levels (see Table 5). All subsequent dosing of BAX 802 should be preceded by measurement of residual FVIII levels and dose adjustments must be based on the most recent residual FVIII activity levels.

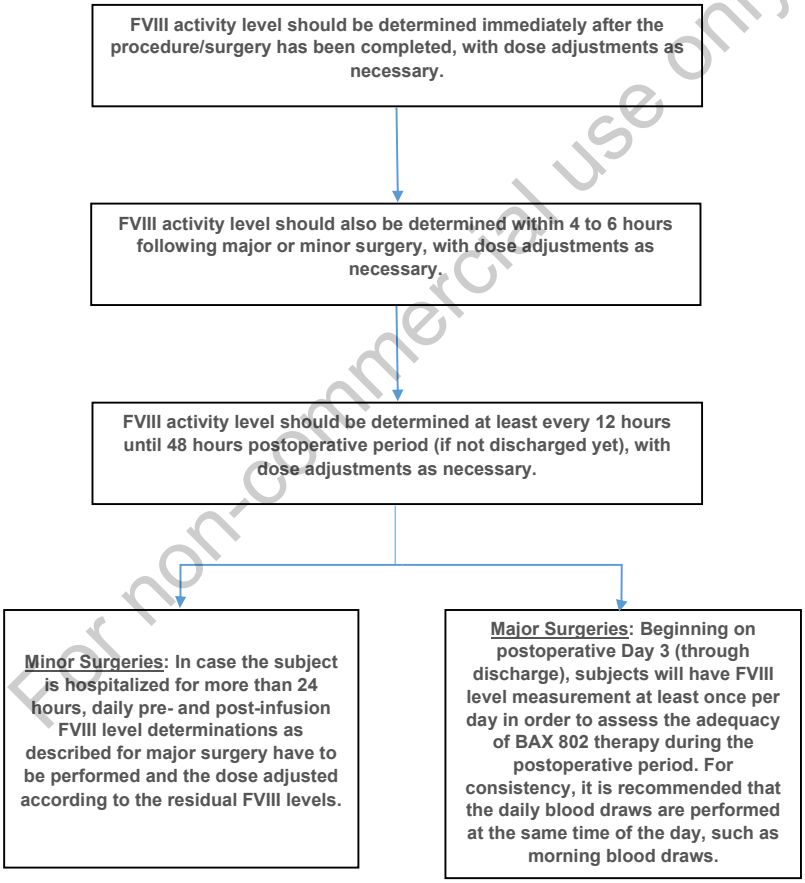
Note: Although peak levels above 200% may be achieved, it is recommended that the plasma levels of FVIII are not sustained above 200% of normal.

Note: Dose adjustments should not be based on activated partial thromboplastin time (aPTT) values.

8.7.3.3.3 Postoperative Dosing

All surgeries/procedures are to have FVIII levels monitored per the diagram in Figure 1:

Figure 1
Postoperative FVIII Monitoring



More frequent monitoring of FVIII activity is advised in subjects who have baseline anti-pFVIII inhibitor titers of ≥ 0.6 BU.

All subsequent dosing of BAX 802 must be preceded by measurement of residual FVIII levels pre-dose and FVIII level measurement 30 ±5 minutes post-dosing.

Note: It is strongly advised that frequency and/or dose of BAX 802 should be increased in order to achieve the recommended FVIII trough levels as per Table 5. The dose of BAX 802 could be increased up to 200 U/kg and the frequency of BAX 802 infusions could be increased up to every 2 hours.

After the initial loading dose, optional re-dosings 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.

It is recommended that the FVIII trough levels are within the range targeted for major surgery during the treatment period as per Table 5. Dosing adjustments based on aPTT values are not allowed.

Note: It is strongly advised that frequency and/or dose of BAX 802 should be increased in order to achieve the recommended FVIII trough levels. The dose of BAX 802 could be increased up to 200 U/kg (although peak levels above 200% may be achieved, it is recommended that the plasma levels of FVIII are not sustained above 200% of normal). The frequency of BAX 802 infusions could be increased up to every 2 hours based on the investigator's clinical judgement together with the measured FVIII levels. If expected FVIII activity levels are not attained after reasonable repeated high doses of BAX 802 (three [3] repeats recommended), physicians should consider the use of rescue medication as per Section 10.6.

Any modifications of the FVIII maintenance plan that are deemed necessary during the postoperative period will be at the discretion of the Investigator and will be documented on the CRFs.

At a minimum, a blood sample for FVIII determination must be drawn prior to any supplemental unscheduled FVIII infusion and 30 ±5 minutes post-dosing.

Note: Since the BAX802 dosing could be as frequent as every 2 hours, getting the pre- and post-dose FVIII level results in real time might not be operationally feasible for all the BAX802 infusions. The sites are recommended to obtain blood samples for both the pre- and post-dose FVIII level to permit FVIII measurements for all BAX802 infusions. However, in cases where the FVIII activity results are not available because of the time of day/night of the frequent infusions, the physicians are not required to wait for all the FVIII level results for dose adjustments, but should employ the FVIII assay results when available for subsequent dosing, thus utilizing the most recent peak and trough FVIII activity levels available together with clinical judgement for dosing decisions.

8.7.3.3.4 Dosing for Unrelated/Surgical Site Bleeding Episodes during the Postoperative Period

Unrelated bleeding episodes and surgical site bleeding episodes are defined in Section 11.2.3.

The BAX 802 dosing regimen for treatment of these bleeding episodes will be based on the guidelines in Table 6. These guidelines may be adjusted by the Investigator based upon his or her clinical judgment.

Table 6
BAX 802 Treatment Guidelines for Unrelated/Surgical Site Bleeding Episodes

Type of Bleeding Episode	Recommended FVIII Level (%)	BAX 802 Dose
Minor Early hemarthrosis, mild muscle bleeding, or mild oral bleeding, including, epistaxis	20% to 40%	Required dose (U) = [body weight (kg) × desired FVIII rise[a] (U/dL or % of normal)]/ 1.2 (U/kg per U/dL) Titrate subsequent doses to maintain recommended FVIII trough levels and individual clinical response until the bleeding resolves.
Moderate Moderate bleeding into muscles, bleeding into the oral cavity, definite hemarthrosis, and known trauma	30% to 60%	
Major Significant gastrointestinal bleeding, intracranial, intra-abdominal, or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces or iliopsoas sheath, fractures, head trauma	60% to 100%	

[a] If the most recent residual FVIII activity level is from the measurement performed ≤ 4 hours of the bleeding episode, use this value to calculate desired FVIII rise. If the most recent residual FVIII activity level is from the measurement performed > 4 hours of the bleeding episode, the desired FVIII rise should be equivalent to the recommended FVIII level for that type of bleeding episode (as described in the column to the left).
Note: It is recommended that the plasma levels of FVIII do not exceed 200% of normal.

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

Repeat infusions of BAX 802 can be administered to treat these bleeding episodes, as per Investigator's discretion.

When bleeding is controlled, additional infusions of BAX 802 to maintain hemostasis are permitted, if required. Infusions given to treat and control the unrelated bleeding episode should be documented in the CRF.

If the subject cannot continue receiving the IP at the study site, (e.g., because the clinic is closed on weekends or subject cannot travel to the site), follow-up treatment, if any, should proceed with SOC products as per Investigator's discretion.

Note: IP (BAX 802) will not be dispensed to the subjects for in-home use.

For a detailed description of bleeding episodes into different sites see Supplement 20.6.

8.7.4 Thrombosis Prophylaxis and Topical Hemostatics

Commercially available gelatin sponges, topical thrombin, fibrin sealants, absorbable collagen preparations or anti-fibrinolytics (e.g., tranexamic acid, ε-amino caproic acid) may be used according to each institution's SOC. Details, including the dose, of all adjunctive hemostatic medication used will be recorded in the CRFs designed for this study and the reason for use given.

Thrombosis prophylaxis can be administered at the discretion of the Investigator according to the SOC of each institution and recorded into the respective CRF. Thrombosis prophylaxis should preferably consist of mechanical measures such as intermittent pneumatic compression (IPC), compression stockings and early mobilization. Pharmacologic thrombosis prophylaxis such as low molecular weight heparin (LMWH) may be considered for certain surgical interventions such as major orthopedic surgery after careful evaluation by the Investigator of the potential risks and benefits.

8.7.5 Investigational Product Accountability

The Investigator will ensure that the IP(s) 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(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. The IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center, as applicable per study design). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) 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(s) 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, 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.

No data will be entered directly onto the case report form (CRF).

For additional information on study documentation and CRFs, see Section 17.2.

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 requires a major or minor elective surgical, dental or other invasive procedure
2. Subject is male and ≥ 12 to ≤ 75 years old at the time of screening
3. Subject has provided signed informed consent (and assent for adolescent subjects, as applicable) in accordance with local regulatory requirements
4. Subject has severe (FVIII level < 1%) or moderately severe (FVIII level ≤ 2%) CHA with inhibitors to hFVIII of ≥ 0.6 BU, as tested at screening at the central laboratory
5. Subject is not currently receiving or has recently received (< 30 days) ITI therapy
6. Subject has a Karnofsky performance score of ≥ 60 at screening
7. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm3 at screening
8. Subject is hepatitis C virus negative (HCV-) by antibody or polymerase chain reaction (PCR) testing; or HCV+ with chronic stable hepatitis disease. Positive serologies will be confirmed by PCR testing.
9. Subject is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

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

1. The subject requires emergency surgery
2. Severe chronic liver dysfunction or disease (e.g., ≥ 5 × upper limit of normal [ULN] alanine aminotransferase [ALT], as confirmed by central laboratory at screening or a documented prothrombin time/international normalized ratio [PT/INR] > 1.5)
3. Clinically symptomatic renal disease (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening
4. Anti-pFVIII inhibitor > 10 BU prior to surgery
5. Platelet count < 100,000/µL at screening
6. Subject has another active coagulation disorder, other than hemophilia A, as per the medical history

7. Planned use of α-interferon with or without ribavarin for HCV infected patients or planned use of a protease inhibitor for HIV infected patients. Patients currently taking any of these medications for ≥ 30 days are eligible
8. Known hypersensitivity to rpFVIII, or hamster or murine proteins
9. Subject has an ongoing or recent (within 3 months of screening) thrombo-embolic disease, fibrinolysis or disseminated intravascular coagulation (DIC)
10. Subject has been exposed to an IP 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
11. Subject is unable to tolerate quantity of blood to be drawn for protocol procedures
12. Subject is a family member or employee of the Investigator.

9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) are described in Section 10.7, Section 20.3, and Section 20.4.

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

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

- AEs/SAEs that in the Investigator's or sponsor's opinion, poses an unacceptable risk for continued dosing in the subject
- Participation in another clinical study involving an IP during the course of the study
- The subject experiences a severe anaphylactic reaction
- The subject had uncontrolled hemorrhage that was the result of inadequate therapeutic response despite proper dosing of BAX 802, necessitating rescue therapy with bypassing agents.

10. STUDY PROCEDURES

10.1 Informed Consent

Any patient who provides informed consent or assent, as applicable (i.e., signs and dates the informed consent form (ICF) and assent form, if applicable) is considered a subject in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (241502) to be provided by the sponsor, 3-digit number study site number (e.g., 002) to be provided by the sponsor, and 3-digit subject number (e.g., 003) reflecting the order of providing informed consent. For example, the third subject who signed an ICF at study site 002 will be identified as Subject 241502-002003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure.

All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

Subjects who fail screening due to a single laboratory test result that does not meet eligibility criteria may have that laboratory test repeated at the discretion of the Investigator. This will include a repeat of only the failed assessment; complete re-screening will not be necessary. In these cases, a new SIC is not required; the subject will maintain their original SIC. The repeat of a screening assessment is allowed once. A repeat assessment must take place within 42 days of the initial screening for any subject requiring repeat of a screening assessment. If this timeframe is exceeded, then all screening assessments must be repeated and the subject assigned a new SIC. Exemptions are possible for administrative reasons and have to be approved by the sponsor. Subjects with an inadequate interval between screening and prior IP drug (other than BAX 802) administration or prior participation in a drug or device study (i.e., 30 days), may be re-screened only once and only when the required interval is reached.

The screening assessment should be performed within 45 days prior to the planned elective surgery.

The overall study design is illustrated in Supplement Figure 2. Details on the procedures to be performed at each study visit, including screening, can be found in Supplement 20.3 and Supplement 20.4.

10.4 Study Periods

The study will be divided into 5 periods:

1. Screening
2. Preoperative
3. Intraoperative
4. Postoperative
5. End of study

A detailed description of study procedures per study period is provided in Supplement 20.1.

10.4.1 GHEA3 Visit

This visit will be performed at discharge or within 24 to 72 hours after the last perioperative treatment dose of BAX 802 (whichever is earlier). Study procedures will be performed as per Table 9 and blood samples will be collected as per Table 10.

Sites must make every effort to complete 3 independent GHEA assessments (GHEA1, GHEA2, GHEA3) for both minor and major procedures, preferably allowing for as much time as possible to pass between assessments within the windows specified in this protocol. In cases such as minor surgeries/procedures, there might be a possibility that the subject is discharged < 24 hours following the surgery/procedure but continues receiving BAX 802 in hospital (e.g., day hospital) setting. In these cases, the GHEA2 hemostatic efficacy assessment should be performed the following day. Also, the GHEA3 Visit should be performed within 24 to 72 hours after the last perioperative treatment dose of BAX 802. Both GHEA2 and GHEA3 assessments can be performed on the day after the surgery/procedure if the subject does not need any further BAX 802 administration for perioperative management.

10.4.2 Antibody Testing Visit

A visit will be performed between 7 to 14 days after last perioperative dose of BAX 802. Study procedures will be performed as per Table 9 and blood samples will be collected for antibody testing and other tests as per Table 10.

10.4.3 Unscheduled Visit

An unscheduled visit could be performed for events such as antibody testing or management of bleeding episodes.

10.4.4 End of Study Visit

The End of Study Visit will be performed 42 ± 7 days after last perioperative dose of BAX 802.

Note: The End of Study Visit should be performed in ALL subjects who have received at least one dose of BAX 802 during Study 241502. This applies also to subjects who receive dose(s) of BAX 802 and do not undergo surgery and withdraw from the study AND to subjects who receive any rescue medications and subsequently withdraw from the study.

10.5 Medications and Non-Drug Therapies

The following medications are **not** permitted anytime during perioperative period until the last GHEA assessment (GHEA3) has been performed (unless used as rescue medications or used to treat unrelated/surgical site bleeding episodes as specified below):

Medications:

- Hemophilia inhibitor bypassing therapy (recombinant factor VIIa [NovoSeven] within 3 hours or activated prothrombin complex concentrate [aPCC; FEIBA]) within 12 hours prior to initial BAX 802 administration) unless used as a rescue medication (Section 10.6) after failure/study withdrawal or used to treat unrelated/surgical site bleeding episodes (Section 11.2.3).
- Hemophilia medication other than BAX 802.

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

The following medications and non-drug therapies are permitted within 30 days before study entry and during the course of the study:

Medications:

- The management of a serious thrombo-embolic event may require anticoagulant medication and this may need to be administered concurrent with the use of BAX 802 to ensure that a re-bleed or continuing severe hemorrhage does not occur on withdrawal of BAX 802 (see Section 10.6). In such instances the Sponsor's medical monitor should be consulted.
- Any medications deemed necessary by the subject's physician to treat or prevent any medical condition (with the exception of those listed as not permitted)
- Any over-the-counter medication used by the subject to treat symptoms or signs of any medical condition
- Supplemental vitamins and minerals

Non-drug therapies:

- Any non-drug therapy (e.g., physiotherapy) deemed necessary by the subject's physician to treat or prevent any medical condition

10.6 Rescue Medications

Bypassing agents (FEIBA or NovoSeven) can be used as a rescue medication if expected plasma FVIII activity levels are not attained or if bleeding is not controlled despite proper dosing of BAX 802 during the intra- or postoperative period of the study. Note: It is strongly advised that frequency and/or dose of BAX 802 should be increased in order to achieve the recommended FVIII trough levels. The dose of BAX 802 could be increased up to 200 U/kg (although peak levels above 200% may be achieved, it is recommended that the plasma levels of FVIII are not sustained above 200% of normal). The frequency of BAX 802 infusions could be increased up to every 2 hours based on the investigator's clinical judgement together with the measured FVIII levels. If expected FVIII activity levels are not attained after reasonable repeated high doses of BAX 802 (three [3] repeats recommended), physicians should consider the use of rescue medication.

Patients switched to rescue medication are required to come to the End of study Visit 42 ± 7 days following the last perioperative dose of BAX 802.

10.7 Subject Completion/Discontinuation

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

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

Every effort will be made to have discontinued subjects complete the study completion/termination visit preferably 42 ± 7 days following the last perioperative dose of BAX802. If the completion/termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the completion/termination visit. If a subject terminates participation in the study and does not return for the completion/termination visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.3 and Supplement 20.4.

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.

10.8 Procedures for Monitoring Subject Compliance

Subject compliance with the procedures and treatment(s) outlined above will be monitored by direct review of the subject's source data at the sites and evaluated against the protocol requirements. Additionally, electronic edit checks will be performed on all protocol-specified procedures and treatment data that are collected to ensure quality and accuracy. Deviations from the protocol-specified procedures and treatments will be noted in the final study report.

All study procedures are to be performed under the direct supervision of the Investigator/a licensed healthcare professional at the study site, and thus, no separate procedures will be used to monitor subject compliance.

11. ASSESSMENT OF EFFICACY

11.1 Primary Efficacy Endpoint: Global Hemostatic Efficacy Assessment Score

The primary outcome measure is the proportion of all surgical or other invasive procedures with a "good" or "excellent" response measured by GHEA. The GHEA score is composed of 3 individual categorical ratings (GHEA1, GHEA2, GHEA3) which will be added together to form the total GHEA score according to Table 1 (see Section 8.4.1).

11.2 Secondary Efficacy Endpoints

11.2.1 Blood Loss

The observed versus predicted (recorded prior to surgery) operative blood loss will be described for the period from initiation of the intervention to discharge or 24 to 72 hours after the last perioperative treatment dose of BAX 802 (whichever is first), as applicable.

Prior to the surgery, the surgeon/Investigator will predict the estimated volume (in 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 and from completion of the procedure until approximately 24 hours post-surgery and for the overall perioperative time period (assessed at discharge or 24 to 72 hours after the last perioperative treatment dose of BAX 802). The expected normal/average, and maximal blood loss and transfusion requirement estimate will be timestamped into the source documentation and/or blood loss form prior to the surgery, and then transferred into the CRF. No changes will be allowed to these estimates after the surgery.

The intraoperative blood loss will be measured by determining the volume of blood and fluid removal through suction into the collection container (waste box and/or cell saver) and the estimated blood loss into swabs and towels during the procedure, per the anesthesiologist's record.

Postoperatively, blood loss will be determined by the drainage volume collected, which will mainly consist of drainage fluid via vacuum or gravity drain, as applicable. In cases where no drain is present, blood loss will be determined by the surgeon's clinical judgment, as applicable or entered as "not available".

11.2.2 Blood Transfusions

The type and volume (in mL) of blood products (e.g., whole blood, red blood cells, platelets and plasma) will be recorded from initiation of the intervention to discharge or 24 to 72 hours after last perioperative treatment dose of BAX 802 (whichever is earlier). Furthermore, also salvage of blood obtained from autologous transfusion systems, (e.g., cell savers) will be recorded. In addition, the type and volume of fluid replacement and volume expanders will be recorded as concomitant medication (e.g., volume of salvaged blood, red blood cells, platelets and other blood products transfused).

11.2.3 Bleeding Episodes

[redacted], until the time of discharge or until the subject resumes his previous treatment regimen, whichever is later.

Any subject who is deemed to have excessive, unexplained bleeding will have blood drawn for measurement of FVIII levels.

Bleeding episodes will be classified as follows:

- Unrelated bleeding episodes: an unrelated bleeding episode is defined as any bleeding occurring at a different anatomical site than the surgery site during the postoperative period.
- Surgical site bleeding episodes: Surgical site bleeding episodes are any bleeding at the surgical/procedure site which occurs after the GHEA3 assessment has been performed.

These bleeding episodes will be treated as follows:

- If these unrelated bleeding episodes or surgical site bleeding episodes occur during the subject's stay in hospital, it is recommended that subjects are treated with BAX 802. BAX 802 will be dosed as per the most recent residual FVIII activity level and clinical judgment using the dosing regimen provided in Table 6 [Required dose = body weight (kg) × desired FVIII rise (U/dL or % of normal)]/ 1.2 (U/kg per U/dL)]. All subsequent dosing of BAX 802 should be preceded by measurement of residual FVIII levels and dose adjustments must be based on the most recent residual FVIII activity levels.

- If these unrelated bleeding episodes or surgical site bleeding episodes occur after the subject has been discharged, subjects may be treated with BAX 802 or SOC, as per Investigator's discretion. Note: IP (BAX 802) will not be dispensed to the subjects for in-home use.

An unscheduled visit could be performed for the management of bleeding episodes.

11.2.4 BAX 802 Administration

The daily and total weight-adjusted administration of BAX 802 per subject will be recorded.

11.2.5 Hemostatic Efficacy Rating for Treatment of Unrelated/Surgical Site Bleeding Episodes

An unrelated bleeding episode is defined as any bleeding occurring at a different anatomical site than the surgery site during the postoperative period. Surgical site bleeding episodes are any bleeding at the surgical/procedure site which occurs after the GHEA3 assessment has been performed. These bleeding episodes will be treated as per Section 11.2.3.

If subject is treated with BAX 802 for unrelated bleeding episodes or surgical site bleeding episodes, the subject will rate the severity (minor, moderate, or major) of the bleeding episode and will rate the overall treatment response at 24 ±2 hours after the initiation of treatment and at the resolution of bleed (if not resolved within 24 hours) using a 4-point efficacy rating scale (Table 7). Since the efficacy rating is based to a large degree on cessation of pain, the Investigator/subject shall, particularly in the event of injury-related bleeding into ≥ 1 location, consider the injury-related symptoms when performing the efficacy rating 24 hours after initiating treatment and at resolution of bleed. Data should be collected as an unscheduled visit.

As per Table 5, multiple infusions of BAX 802 may be administered for the treatment of a bleeding episode. The overall response to all infusions combined is the rating that will be recorded at resolution of bleed.

Table 7
Efficacy Rating Scale for Treatment of Unrelated/Surgical Site Bleeding Episodes

Excellent	Full relief of pain and/or cessation of objective signs of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution.
None	No improvement or condition worsens.

As per Table 5, multiple infusions of BAX 802 may be administered for the treatment of a bleeding episode. The overall response to all infusions combined is the rating that will be recorded at resolution of bleed.

11.3 Factor VIII Activity

Blood will be obtained for assessment of FVIII activity at screening (tests to be performed at the **central laboratory**). Results from **local laboratory** will be used to make any dosing decisions.

Blood will be obtained for assessment of FVIII activity for patient management purposes at the following time points (tests to be performed at the **local laboratory**, with additional back-up samples to be tested in 1 batch at the **central laboratory**):

- Within 30 minutes prior to the administration of the initial loading dose preoperatively and 30 ±5 minutes post-infusion. If re-dosing with BAX 802 is required to obtain the required FVIII levels, an additional blood sample needs to be drawn 30 ±5 minutes following the re-dosing with BAX 802.
- Postoperatively until the GHEA3 visit: daily within 30 minutes prior to the infusion of BAX 802 and 30 ±5 minutes post-infusion.
  Pre- and post-dosing blood draws for FVIII activity level determination should also be performed for each BAX 802 administration.
- FVIII activity will also be assessed if the subject has excessive, unexplained bleeding at any time intra-or postoperatively, or whenever deemed necessary according to the institution's SOC.

11.3.1 Blood Sampling and Processing for FVIII Analysis

At each blood sampling time point whole blood will be collected in blood sampling tubes will be collected in S-Monovette® tubes (Sarstedt, Nümbrecht, Germany) containing 3.2% trisodium citrate, or equivalent blood drawing equipment (e.g., Vacutainer tubes), and immediately mixed. The citrated whole blood samples will be capped and transported at room temperature (i.e., 20 to 25°C) to the local clinical laboratory for centrifugation, processing, and storage. Monovettes must be kept in an upright position at all times to avoid leakage.

All samples taken through 6 hours post-dosing will be collected from an extremity other than that used for the infusion of study product. Thereafter, either extremity may be used to obtain samples.

If the subject has a central 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 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 sample.

All citrated plasma samples will be stored and shipped to the central laboratory at ≤ -70°C for testing.

All back-up samples collected during the perioperative period will be shipped to the central laboratory as soon as possible in 1 batch and analyzed, as needed.

Blood samples will be analyzed for FVIII activity (1-stage clotting assay and the chromogenic assay) at the central laboratory. The 1-stage FVIII activity assay will serve as the primary assay; the chromogenic assay of FVIII activity will be used to provide supportive data. Local laboratories are expected to use a 1-stage clotting assay.

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 (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that at any dose meets 1 or more of the following criteria:

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

- Thrombo-embolic events (e.g., stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism).
- The confirmed development of de-novo anti-pFVIII inhibitory antibodies or increases of > 10 BU in pre-existing titers of anti-pFVIII inhibitory antibodies (see Section 12.1.1.1.1)

Planned hospitalization for any study procedures as per the protocol will not be considered as an SAE.

12.1.1.1.1 Inhibitory Serious Adverse Events

The development of de-novo anti-pFVIII inhibitory antibodies (≥ 0.6 BU) must be confirmed with a second blood draw 7 to 14 days after the initial confirmed positive de novo result (or repeat testing of original sample if a second draw is not possible). Confirmation of de novo inhibitory antibodies or a confirmed increase of > 10 BU in pre-existing titers of anti-pFVIII inhibitory antibodies must be reported as a SAE within 24 hours, and followed up.

Increases in pre-existing titers of anti-pFVIII inhibitory antibodies will require a second confirmatory test 7 to 14 days after the initial confirmed positive increase (or repeat testing of original sample if a second draw is not possible). If the protocol-defined significant increase (> 10 BU) is confirmed, it will be reported as an SAE.

Safety will be further monitored by the Investigator and medical monitor to evaluate the clinical significance of the inhibitor level. Although the development of, or increase in, anti-pFVIII inhibitory antibody titers may not necessarily indicate a failure of response to BAX 802, the inhibitor levels and patient response will be closely monitored and an alternative therapy will be considered for lack of efficacy, if applicable.

12.1.1.2 Suspected Unexpected Serious Adverse Reaction

Any suspected adverse reaction to study treatment that is both serious and unexpected.

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

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

Once determined to meet the criteria for a SUSAR, an SAE should be submitted to regulatory agencies expeditiously.

12.1.1.3 Non-Serious Adverse Event

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

12.1.1.4 Unexpected Adverse Events

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). "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 product, but are not specifically mentioned as occurring with the particular product under investigation. The expectedness of AEs will be determined by the sponsor using the Company Core Data Sheet for OBIZUR as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.

12.1.1.5 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 are collected under other study endpoints and thus are not reportable on the AE CRF, nor will they be included in the analysis of AEs:

Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be assessed as part of the efficacy assessments. However, the Investigator may decide that the event is an AE if the event also would have occurred in a normal patient under the same circumstances. If a bleeding episode was caused by an injury, the injury will be reported as an AE. All bleeding episodes must be entered in the bleeding event CRF.

All other/Each AE from the first IP exposure until study completion or 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 (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, or unknown) and if applicable action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

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

If an Investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the provided SAE Report 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, for example, assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the Investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs

- Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).

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

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

12.1.2.3 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Table 9) and Section 12.1.

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

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the IP, must be reported immediately (within 24 hours of the study center's first knowledge of the event).

Any SAEs must be reported using the paper SAE Report Form to meet the 24 hour timeline requirement (for contacts and instructions refer to the SAE Report Form).

The initial SAE information reported on the applicable SAE Report Form must at least include the following:

- Protocol number
- Subject identification number and demographics (gender, age at onset of event and/or date of birth)
- IP exposure
- Medical Term for Event (Diagnosis preferably)
- Description of the (S)AE, including:
  - Date of onset
  - (S)AE treatment (drug, dose, route of administration)
  - Causal relationship by the Investigator
  - Measures taken (i.e., action taken regarding IP in direct relationship to the AE)
- Seriousness criteria (i.e., death, life-threatening, or other criterion)
- Cause of death
- Autopsy findings (if available)
- Name, address, fax number, email, and telephone number of the reporting
- Investigator

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 (ECs) and relevant competent authority(s) are notified of the urgent safety measures 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 (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the AE CRF (and SAE Report Form if CRF is not available). These events will not be considered as SAEs and will not be included in the analysis of SAEs.

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

- Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be assessed as part of the efficacy assessments. If a bleeding episode was caused by an injury, the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (e.g., abrasion of skin). Therefore, any hemophilia-related event (e.g., hemarthrosis [presenting as swelling, pain, and decreased range of motion], bruising, hemorrhages, or pain at bleeding episode site) will not be reported as AEs. However, the Investigator may decide that the event is an AE if the event also would have occurred in a normal patient under the same circumstances.

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.** The NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g., reconstitution difficulty
- Missing components

- Damage to the product or unit carton
- A mislabeled product (e.g., 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.

Medical history will include the collection of hemophilia history, bleeding episode history, and history of aPCC or rFVIIA usage for 6 months prior to screening. Relevant medical and surgical history and all medications taken 3 months prior to screening will also be collected.

All medications taken and non-drug therapies received within 3 months before providing informed consent until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Table 9), 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 12.1.1.5), 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

Clinical chemistry and hematology assessments will be performed on whole blood and EDTA-anticoagulated serum, respectively, at the central laboratory. Details of blood sampling volumes are presented in the laboratory manual and master ICF.

12.7.1 Hematology, Clinical Chemistry, and Urinalysis

The hematology panel will consist of complete blood count (hemoglobin, HCT, erythrocytes [i.e., red blood cell count], and leukocytes [i.e., white blood cell count]) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

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

The frequency of blood draws for clinical and hematology assessments is provided in Table 10.

The urinalysis panel will consist of pH, protein, ketones, glucose, bilirubin, blood, urobilinogen, specific gravity by dipstick and microscopy if any findings are abnormal.

Urine will be obtained for assessment of urinalysis parameters as per Table 10.

12.7.2 Viral Serology

Viral serology testing will include HIV-1 and HIV-2 antibody, HAV (immunoglobulin M [IgM] and total antibodies), hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), HCV antibody, and parvovirus B19 (IgM and immunoglobulin G [IgG] antibodies). The HIV and HCV titer will be confirmed by PCR for all subjects reported as HIV and HCV positive. All viral serology assessments will be performed at screening. Any positive HBsAg test will be repeated using a new blood sample.

12.7.3 Immunogenicity

Immunogenicity assessments will include anti-pFVIII and hFVIII binding (IgG and IgM) and inhibitory antibodies and anti-BHK binding antibodies.

Blood samples will be collected for the assay of anti-pFVIII and hFVIII binding and inhibitory antibodies and anti-BHK binding antibodies at the times indicated in Table 9 and Table 10.

All FVIII assays related to study subject management decisions by the Investigator will be performed at the Investigator's local laboratory.

A central reference laboratory will perform assays (anti-pFVIII, anti-hFVIII, and anti-BHK) on samples taken at the times indicated in Table 9 and Table 10.

Binding antibodies to human and porcine FVIII (both IgG and IgM) and binding antibodies to BHK proteins will be analyzed using validated enzyme-linked immunosorbent assays (ELISAs) using a multi-tiered approach consisting of screening assay, titer determination and confirmation of specificity. [redacted]

The assessment of inhibitory antibodies to pFVIII and hFVIII will be determined using a Bethesda assay (with the Nijmegen modification if possible). Further details on blood collection, tube preparation and shipment will be provided in the Laboratory Manual.

12.7.4 Assessment of Laboratory Values

12.7.4.1 Assessment of Abnormal Laboratory Values

The Investigator's assessment of each laboratory value will be recorded on the CRF. For each abnormal laboratory value, the Investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the Investigator will indicate if the value constitutes a new AE (see definition in Section 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 12.1.1.5), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the Investigator will indicate the reason, i.e., because it is due to a preexisting disease, due to a laboratory 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.

12.7.5 Backup Samples and Biobanking

Backup samples taken and stored short-term may be used for re-testing, follow-up of an AE(s) or other test results (such as FVIII activity and antibody testing), and/or assay development.

After study testing is completed, the remaining samples may be stored in a coded form for no more than 2 years after final study report completion and then the samples will subsequently be destroyed.

For this study, no samples will be taken or stored long-term in a biobank for future analyses.

12.8 Vital Signs

Vital signs will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), systolic and diastolic blood pressure (mmHg). height (in or cm), and weight (lb or kg).

Height and weight is measured only once at screening.

All other vital signs will be measured at screening and within 30 minutes before and 30 ±5 minutes after administration of IP, at least on Day1, 2, 3 and 7 until GHEA3 Visit, at GHEA3 Visit, the antibody testing Visit, at any unscheduled assessments, and at the End of Study Visit. Blood pressure will be measured when subjects are in the supine position.

Vital sign values are to be recorded on the 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.

12.9 Karnofsky Performance Test

The Karnofsky Performance Test is a status scale (0 to 100) utilized to measure the level of activity and medical care requirements in subjects. It is an Investigator based assessment of patient status which evaluates the subjects' ability to carry on normal life activities, as well as the symptoms of their disease.[19] Subjects will be scored using this scale at screening.

12.10 Special Treatment Considerations

Patients will be screened for eligibility in the study as described in the inclusion/exclusion criteria (Section 9.1 and Section 9.2), and will be informed of the study specific restrictions and requirements of the study. Patients who are not willing to comply with the study requirements and restrictions of the study will not be eligible for enrollment.

All biological agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include, but are not limited to:

- skin rash
- pruritus (itching)
- urticaria (hives)
- angioedema (e.g., swelling of the lips and/or tongue)
- anaphylactic reaction.

Proteins may also cause redness, itching, swelling, or pain locally at the infusion site.

Sometimes, these reactions can be life-threatening. Therefore, all patients should be closely monitored for signs or symptoms that could result from such reactions, educated on the signs or symptoms of these types of reactions, and instructed to contact the study site immediately if any of the symptoms are experienced following an injection.

If a patient experiences an acute allergic/hypersensitivity reaction after an injection of IP, he should be managed appropriately and given instruction to receive relevant supportive care. Additionally, for an event judged by the Investigator to be a potential systemic allergic/hypersensitivity reaction, blood samples will be collected for anti-pFVIII, anti hFVIII, and anti-BHK binding antibodies. Serious adverse events related to development or worsening of inhibitors are described in Section 12.1.1.1.1.

Patients who experience a potentially severe allergic reaction will be discontinued from study drug, they will complete an End of Study Visit, and will be monitored for stabilization, or resolution of the AE. Premedication to prevent allergic reactions will not be permitted as severe allergic reactions are an outcome measure for this study.

13. STATISTICS

All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the statistical analysis plan (SAP).

13.1 Sample Size and Power Calculations

The total sample size for the study is 12 evaluable subjects, which includes at least 12 surgeries/procedures in 12 evaluable male subjects (at least 5 major surgeries/procedures in 5 evaluable subjects) and at least 2 of the 12 subjects are adolescents (≥ 12 to < 18 years old). The sample size, as defined in the protocol, was chosen to provide sufficient evidence of safety and effectiveness for this indication and is not based on statistical considerations.

Evaluable subjects are defined as subjects who met all study entry criteria and who had at least 1 hemostatic efficacy assessment as per Section 8.4.1.

13.2 Analysis Sets

Classification into the analysis sets will be conducted prior to the database lock.

13.2.1 Safety Analysis Set

The safety analysis set (SAS) will be comprised of all subjects who received any amount of BAX 802.

13.2.2 Efficacy Datasets

13.2.2.1 Full Analysis Set

The FAS will be comprised of all surgeries with at least 1 available hemostatic assessment.

13.2.2.2 Per-Protocol Analysis Set

The per-protocol (PPAS) analysis set will be comprised of all surgeries with evaluable ratings for all 3 perioperative hemostatic efficacy assessments, whose subjects met all study entry criteria and had no major protocol violations that might impact hemostatic efficacy assessments.

13.3 Handling of Missing, Unused, and Spurious Data

A subject who withdraws prior to the last planned observation in a trial period will be included in the analyses up to the time of withdrawal.

For surgeries with ≤ 2 missing hemostatic assessments that did not necessitate rescue therapies, the rating of "fair" will be imputed for the missing assessment. These surgeries will be included in the FAS.

13.4 Methods of Analysis

For qualitative parameters, the population size (N for sample size and n for available data) and the proportion (of available data) for each class of parameters will be presented. Quantitative parameters will be summarized by the population size (N for sample size and n for available data), mean, standard deviation, median, minimum, and maximum values.

13.4.1 Primary Outcome Measure

The primary efficacy measure will be the overall assessment of hemostatic efficacy assessed intraoperatively and at postoperative Day 1 (postoperative period, i.e., from end of surgery to 24 ±6 hours post-surgery) by the surgeon and perioperatively at 24 to 72 hours after the last perioperative treatment dose of BAX 802 or discharge (whichever is earlier) by the Investigator (hemophilia physician), and where possible, by both the Investigator and the operating surgeon (assessment by both is strongly recommended), and will be the sum of intraoperative, postoperative, and perioperative GHEA scores as rated "excellent", "good", "fair" or "none". In cases where there are differing assessments, the Investigator's assessment will be used.

Wherever possible (except for intraoperative assessment), bleeding should be assessed by both operating surgeon and Investigator. To achieve the hemostatic efficacy success criteria, the study needs to achieve a ≥ 70% rate of hemostatic efficacy assessments with an "excellent" or "good" outcome in at least 12 procedures.

Hemostatic efficacy success is defined as an "excellent" or "good "outcome for ≥ 70% of hemostatic efficacy assessments.

Due to the possibility of a subject undergoing multiple surgeries, the statistical analysis of the primary outcome measure will be reported on the by-surgery level (i.e., not by the number of subjects). In cases where two or more surgical procedures are performed in the same intraoperative settings (under the same anesthesia, e.g., bilateral knee replacement) the surgery will be counted as one surgery.

Blood loss assessment from those surgeries will be assessed as one. In the event that the subject is planning to have additional surgery in the future, they will need to complete the study and be re-screened again (if > 3 months from the screening) to ensure that they continue to meet the eligibility criteria.

Point estimates and corresponding 2-sided exact Clopper-Pearson confidence intervals (CIs) at the 95% confidence level will be calculated for the rate of hemostatic efficacy assessments with excellent/good outcome for descriptive purposes.

The proportion of all surgeries and of all major surgeries with hemostatic success will be reported along with exact 95% CIs. A treatment success will be defined as a rating of excellent or good.

The primary efficacy analysis will be based on the FAS population. As a supportive analysis, the same analyses will also be carried out on the PPAS population.

A sensitivity analysis based on the first surgery will be performed if more than 20% of subjects have multiple surgeries. Any blood loss which is considered as unrelated bleeding (defined as any bleeding occurring at a different anatomical site other than the surgery site during the postoperative period, see Section 11.2.5) will not be taken into account for while making assessment of hemostatic efficacy for the primary efficacy measure.

13.4.2 Secondary Outcome Measures

13.4.2.1 Secondary Hemostatic Efficacy Analysis

Secondary outcome measures will be reported at the surgery level rather than the subject level. Descriptive statistics will be used to summarize the actual blood loss and transfusion requirements.

The summary of average daily and total weight-adjusted doses (average through postoperative 24 to 72 hours after last perioperative treatment dose of BAX 802 or discharge [whichever is earlier]) of BAX 802 per subject as well as the occurrence of bleeding episodes will be provided using descriptive statistics.

The proportion of major surgeries with good or excellent hemostatic score together with its 2-sided 95% CI will be reported for descriptive purposes.

The secondary efficacy analysis will be performed on the FAS only.

13.4.2.2 Safety Analysis

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by presenting the number and proportion of subjects having any AE, having an AE in each system organ class, and having each individual AE as reported by preferred term. In the summaries, AEs will be counted only once per patient. If a patient reports the same AE more than once, it will be counted with its worst severity and closest relationship to the study product.

The number of subjects who experienced SAEs and the number of SAEs will be tabulated. In addition, the number of subjects who experienced AEs related to IP and the number of IP-related AEs will be tabulated and subcategorized for thrombo-embolic events, inhibitory and total binding antibodies (IgG and IgM) to pFVIII and hFVIII, and binding antibodies to BHK proteins.

A listing of all AEs will be presented by subject identifier, age, preferred term, and reported term of the AE, duration, severity, seriousness, action taken, outcome, causality assessment, onset date, stop date, and medication or non-drug therapy to treat the AE. An overview table for AEs will be provided, presenting the number of AEs, the number of subjects with AEs and the corresponding percent of subjects in total, and by seriousness and relationship to study treatment. An additional summary table will present the total number of (mild, moderate, severe) AEs by system organ class and preferred term with relationship to IP.

Summary statistics over time will be presented for the continuous laboratory parameters. Descriptive statistics of changes from baseline (prior to BAX 802 loading dose before the surgery) by study visits will also be presented.

A frequency table of results of categorical laboratory parameters will be produced. Furthermore, laboratory abnormalities will be analyzed by shift tables where each subject will be counted only once with the worst grade in the summary tables.

All laboratory data will be listed with abnormal values.

Vital signs assessments as well as the corresponding changes from baseline will be summarized descriptively at each scheduled or unscheduled assessment.

The safety analysis will be based on the SAS.

13.4.1 Exploratory Outcome Measures

[redacted]

[redacted]

[redacted]

[redacted]

Further details will be included in the SAP.

13.5 Planned Interim Analysis of the Study

No interim analyses are planned for this study.

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 Institutional Review Board (IRB) or Ethics Committee (EC), and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the Investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the CTA.

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 national and local regulatory requirements as described in the CTA. The Investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "Investigator" as used in this protocol as well as in other study documents, refers to the Investigator or authorized study personnel that the Investigator has designated to perform certain duties. Sub-Investigators or other authorized study personnel are eligible to sign for the Investigator, except where the Investigator's signature is specifically required.

15.1.1 Investigator Report and Final Clinical Study Report

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

15.2 Training

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

15.3 Monitoring

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

15.4 Safety Monitoring

The safety of the subjects in this study shall be monitored by an external DSMB comprised of experts in the field of hemophilia research and clinical care.

The DSMB will review safety data at predefined intervals and make recommendations to the study team on study conduct including dose escalation and modifications to study plan. Details of the composition and responsibilities of the DSMB will be provided in a DSMB charter.

15.5 Auditing

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

15.6 Non-Compliance with the Protocol

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

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

15.7 Laboratory and Reader Standardization

Not applicable; a central laboratory/reader will be used for all clinical assessments. Local laboratories are requested to provide their laboratory specifications for each assay used.

16. ETHICS

16.1 Subject Privacy

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

16.2 Ethics Committee and Regulatory Authorities

Before patients participate in this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information 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(s) approval, as described in the CTA.

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

16.3 Informed Consent

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

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

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

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

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, screening information, CRFs, SAERs, laboratory reports (if applicable), and data clarifications requested by the sponsor.

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

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

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

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

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 CTA.

19. PUBLICATION POLICY

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

20. SUPPLEMENTS

20.1 Procedures per Study Period

Table 8
Summary of Required Procedures for Baxalta Clinical Study 241502

1. Screening

Written Informed Consent must be obtained prior to any study-related procedures

Screening activities should be performed within 45 days prior to the planned elective surgery.

The following screening procedures are required:

- Eligibility evaluation (review of inclusion/exclusion criteria)
- Relevant medical and surgical history (including Hemophilia history, bleeding episode history, history of aPCC or rFVIIA usage for 6 months prior to screening)
- Review of concomitant medications/non-drug therapies and all medications taken 3 months prior to screening
- Physical examination (see Section 12.6)
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measure body weight and height; see Section 12.8)
- Karnofsky performance test assessment (see Section 12.9)
- Clinical laboratory assessments (see Table 10).

Table 8
Summary of Required Procedures for Baxalta Clinical Study 241502

2. Preoperative Procedures

Subjects will return to the study site prior to their scheduled surgery as instructed by site staff. Subjects will undergo the following procedures:

Prior to surgery

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

- Accurate prediction of volume of expected blood loss intraoperatively (from completion of the procedure until approximately 24 hours post-surgery) and for the overall perioperative time period (up to 24 to 72 hours after the last perioperative treatment dose of BAX 802 or discharge), which is to be timestamped into the source documentation and/or blood loss form prior to the surgery.

Loading Dose and Post Dosing Laboratory Assessment

Within 1 to 2 hours before initiating surgery, the subject will receive a loading dose of BAX 802 to raise the plasma level of FVIII to ≥ 80% for major and to ≥ 50% for minor surgical, dental and invasive procedures.

Subjects will undergo the following procedures:

- **Prior to BAX 802 loading dose:**
  - Record AEs, concomitant medications, and non-drug therapy use
  - Physical examination
  - Vital signs (pulse rate, respiratory rate, blood pressure, and temperature)
  - Laboratory Assessments including:
    - Hematology (without differential but including platelets)
    - Clinical chemistry
    - Within 30 minutes before loading dose, blood draw for:
      - FVIII activity
- **BAX 802 loading dose:**
  - Loading dose of BAX 802 to raise the plasma level of FVIII to ≥ 80% of normal for major and to ≥ 50% for minor surgical, dental and invasive procedures. It will be administered within 1 to 2 hours prior to surgery (prior to incision/intubation).
- **After BAX 802 loading dose:**
  - Laboratory assessment of FVIII activity: 30 ±5 minutes after infusion of the loading dose
  - Vital signs (pulse, respiratory rate, blood pressure and temperature) will be recorded 30 ±5 minutes after infusion
  - Confirmation that FVIII is adequate just prior to intubation/incision. Administration of additional dose of BAX 802, if required. If another dose of BAX 802 is necessary, an additional post-infusion FVIII activity determination must be performed 30 ±5 minutes following the infusion.
  - All samples taken through 6 hours post-infusion will be collected from an extremity other than that used for the infusion of study product. Thereafter, either extremity may be used to obtain samples.

The surgery may begin only if FVIII is in target range (Table 5 and Section 8.7.3.3.2).

Throughout: Monitoring of AEs and concomitant medication and non-drug therapy use.

Table 8
Summary of Required Procedures for Baxalta Clinical Study 241502

3. Intraoperative Procedures (end of surgery = Day 0)

During the surgical procedure:

- Record AEs and concomitant medication and non-drug therapy use
- Record blood product usage, (e.g. whole blood, red blood cells, platelets and plasma.
- Administer additional BAX 802 infusions according to the dosing regimen (Table 5)
- Record intraoperative blood loss and transfusion requirements

If the subject has excessive or unexplained bleeding, draw blood for FVIII activity. Treat by whatever means necessary until adequate hemostasis is achieved. If rescue medications become necessary, subjects switching to rescue medication are required to come to the End of study Visit 42 ± 7 days following the last perioperative dose of BAX 802.

After the surgical procedure:

- Record the volume of blood loss during surgery and amount of total blood product usage, (e.g. whole blood, red blood cells, platelets and plasma Assess intraoperative hemostatic efficacy (Global Hemostatic Efficacy Assessment, GHEA1, Table 2) (at the end of surgery)
- Take sample for FVIII activity immediately after surgery completion, with dose adjustments as necessary on the day of surgery (see Section 10.5)
- Take sample for FVIII activity within preferably 4 to 6 hours following surgery, with dose adjustments as necessary on the day of surgery (see Section 10.5)

If the subject has excessive or unexplained bleeding, draw blood for FVIII activity. Treat by whatever means necessary until adequate hemostasis is achieved. If rescue medications become necessary (see Section 10.5), subjects switching to rescue medication are required to come to the End Of study Visit 42 ± 7 days following the last perioperative dose of BAX 802.

Table 8
Summary of Required Procedures for Baxalta Clinical Study 241502

4. Postoperative Procedures (Day 1 to GHEA3 Visit)

- For subjects undergoing major surgery: keep pre-infusion FVIII levels at least at 80% of normal for the first postoperative 72 hours and at least at 50% during postoperative Day 4 to Day 7. It is recommended that the FVIII levels do not fall below 30% from Day 8 until GHEA3 Visit.
- For subjects undergoing minor surgery: keep pre-infusion FVIII levels at least at 50% of normal for the first postoperative 72 hours. It is recommended that the FVIII levels do not fall below 30% from Day 4 onwards (if not yet discharged and GHEA3 not yet performed).

  From Postoperative Day 1 (i.e., the day following the day of the surgical/invasive procedure), and daily until the GHEA3 Visit the following assessments will be performed:

  - Record AEs and concomitant medication and non-drug therapy use
  - Record blood loss on a daily basis and at drain removal, if applicable
  - Record transfusion requirements
  - GHEA:
    - GHEA2 (Table 3): assessment of postoperative hemostatic efficacy of BAX 802 performed at Day 1 by the operating surgeon/Investigator
    - GHEA3 (Table 4): assessment of perioperative hemostatic efficacy of BAX 802 at 24 to 72 hours after the last perioperative treatment dose of BAX 802 or discharge (whichever is earlier) performed by the Investigator, and where possible, also by the operating surgeon

    In cases such as minor surgeries/procedures, there might be a possibility that the subject is discharged < 24 hours following the surgery/procedure but continues receiving BAX 802 in hospital (e.g., day hospital) setting. In these cases, the GHEA2 hemostatic efficacy assessment should be performed the following day. Also, the GHEA3 Visit should be performed within 24 to 72 hours after the last perioperative treatment dose of BAX 802. Both GHEA2 and GHEA3 assessments can be performed on the day after the surgery/procedure if the subject does not need any further BAX 802 administration for perioperative management.
  - Perform physical examination and vital signs as per Table 9.
  - Blood draws for FVIII activity determination and hematology should be performed coincident with an early morning dose to the greatest extent possible.
  - FVIII activity assays at the local and the central laboratories as per Section 8.7.3.3.3. Additional BAX 802 doses will be administered as per Table 5. FVIII activity assays pre infusion (within 30 minutes) and post infusion (30 ±5 minutes) for each IP administration, and at other time points as deemed necessary by the surgeon or Investigator throughout the study
    - 1-stage clotting and chromogenic for the central laboratory
    - 1-stage clotting for local laboratories
  - Samples for laboratory testing will be taken daily during Day 1 to 7 post-surgery and then subsequently once weekly:
    - Hematology
    - Clinical chemistry
- If the subject has excessive or unexplained bleeding, draw blood for FVIII activity. Treat by whatever means necessary until adequate hemostasis is achieved. If rescue medications become necessary, subjects switching to rescue medication are required to come to the End of study Visit 42 ± 7 days following the last perioperative dose of BAX 802.

Table 8
Summary of Required Procedures for Baxalta Clinical Study 241502

- If the subject is discharged from surgical facility on the day of the procedure, he should attend the site on Day 1 to perform the postoperative hemostatic efficacy assessment (Day 1 assessment) and the overall perioperative assessment. In this case, physical examination, vital signs, laboratory assessments, adverse events, and concomitant medications must also be assessed. If the subject is discharged from surgical facility after Day 1 but prior to the overall perioperative assessment, he should return to the site for that assessment as well as the required physical examination, vital signs, laboratory assessments, adverse events, and concomitant medications assessments.

5. GHEA3 Visit

The perioperative hemostatic efficacy assessment (GHEA 3) will be performed 24 to 72 hours after the last perioperative treatment dose of BAX 802 or at discharge, whichever is earlier. In cases such as minor surgeries/procedures, there might be a possibility that the subject is discharged < 24 hours following the surgery/procedure but continues receiving BAX 802 in hospital (e.g., day hospital) setting. In these cases, the GHEA2 hemostatic efficacy assessment should be performed the following day. Also, the GHEA3 Visit should be performed within 24 to 72 hours after the last perioperative treatment dose of BAX 802. Both GHEA2 and GHEA3 assessments can be performed on the day after the surgery/procedure if the subject does not need any further BAX 802 administration for perioperative management.

Procedures to be performed for each subject at GHEA 3 Visit:

- Assessment of blood loss
- Assessment of transfusion requirements
  - Review of concomitant medications/non-drug therapies
  - physical examination
  - AE monitoring
  - Vital signs (body temperature, pulse rate, blood pressure, respiratory rate)
- Clinical laboratory assessments (Table 10)
- Immunogenicity assays:
  - [redacted]
  - Anti-BHK binding antibody titers

6. Antibody Testing Visit

A visit will be performed between 7 to 14 days after the last perioperative treatment dose of BAX802. Study procedures will be performed as per Table 9 and blood samples will be collected for antibody testing and other tests as per Table 10. De novo or clinically significant increases in antibodies will require a confirmatory blood sample collection 7 to 14 days after the initial positive result.

Procedures to be performed for each subject at Antibody Testing Visit:

- Immunogenicity assays:
  - [redacted] (Note: these will be performed only if at least 72 hours must have elapsed since the previous BAX 802 administration)

Anti-BHK binding antibody titers

Table 8
Summary of Required Procedures for Baxalta Clinical Study 241502

7. End of Study [EOS] Visit (42 ± 7 days of last dose of BAX 802)

EOS Visit will be performed 42 ± 7 days following the last perioperative dose of Bax802.

Procedures to be performed for each subject at EOS Visit:

- Assessment of blood loss
- Assessment of transfusion requirements
  - Review of concomitant medications/non-drug therapies
  - physical examination
  - AE monitoring
  - Vital signs (body temperature, pulse rate, blood pressure, respiratory rate)
- Clinical laboratory assessments (Table 10)
- Immunogenicity assays:
  - [redacted]

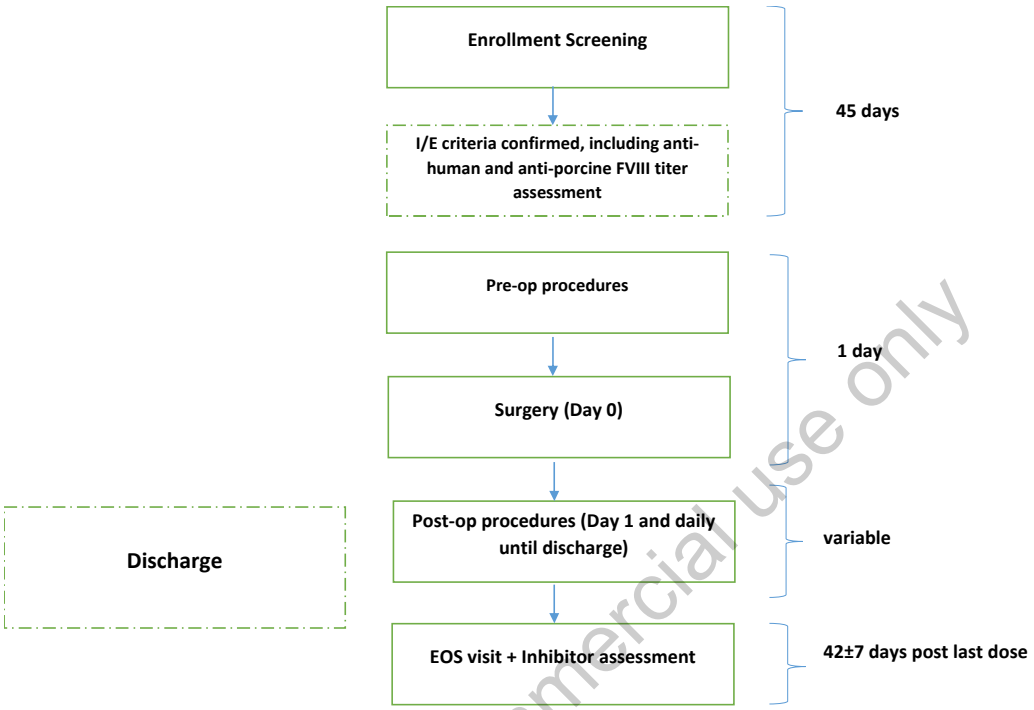
Anti-BHK binding antibody titers

Unrelated Bleeding Episodes During the Postoperative Period:

An unrelated bleeding episode is defined as any bleeding occurring at a different anatomical site than the surgery site during the postoperative period. Refer to Section 11.2.5, Table 9, and Table 10.

20.2 Study Flow Chart

Figure 2
Visit Schedule



20.3 Schedule of Study Procedures and Assessments

Table 9
Schedule of Study Procedures and Assessments

Period	Screening	Preoperative	Intraoperative	Postoperative		End of Study	Procedures for Unrelated/Surgical Site Bleeding Episodes During the Postoperative Period (see Sections 11.2.3 and 11.2.5)[d]
Visit	**Screening**	**Preoperative procedures**	**Intraoperative procedures**	**Postoperative: Daily procedures**	**Antibody Testing Visit[a]**	**End of Study Visit[b]**	
Time point	**Up to 45 days prior to Day 0**	**Day 0 ~60 to 120 minutes prior to surgery**	**Day 0 During surgery**	**Day 1 and daily thereafter until GHEA3[c]**	**7 to 14 days after last perioperative treatment dose of BAX 802**	**42 ± 7 days after last perioperative treatment dose of BAX 802**	
Eligibility criteria, including medical history[e]	X						
Prediction of intraoperative blood loss[f]		X					
Medications and non-drug therapies	X	X	X	X	X	X	X
Physical examination	X	X		X[g] (as required)	X	X	
Adverse events		X	X	X	X	X	X
Laboratory assessments[h]	X	X[i]	X	X[j]	X	X	X
Vital signs[k]	X	X	X	X	X	X	
Karnofsky Performance Test	X						
Approved FVIII maintenance plan		X					

Table 9
Schedule of Study Procedures and Assessments

Period	**Screening**	**Preoperative**	**Intraoperative**	**Postoperative**		**End of Study**	**Procedures for Unrelated/Surgical Site Bleeding Episodes During the Postoperative Period (see Sections 11.2.3 and 11.2.5)[d]**
Visit	**Screening**	**Preoperative procedures**	**Intraoperative procedures**	**Postoperative: Daily procedures**	**Antibody Testing Visit[a]**	**End of Study Visit[b]**	
Time point	**Up to 45 days prior to Day 0**	**Day 0 ~60 to 120 minutes prior to surgery**	**Day 0 During surgery**	**Day 1 and daily thereafter until GHEA3[c]**	**7 to 14 days after last perioperative treatment dose of BAX 802**	**42 ± 7 days after last perioperative treatment dose of BAX 802**	
IP treatment		X (loading dose; Table 5)	X (as required; Table 5)	X (as required; Table 5)			Refer to Table 6
Hemostatic Efficacy Assessments (GHEA1, GHEA2, and GHEA3)			**GHEA1** at the end of surgery as per Table 2	**GHEA2** at 12 to 24 hours (Day 1) as per Table 3 **GHEA3** at 24 to 72 hours after the last perioperative treatment dose of study drug is administered or discharge (whichever is earlier), as per Table 4			At 24 ±2 hours after the initiation of treatment and at the resolution of bleed (if not resolved within 24 hours) using a 4-point efficacy rating scale (Table 7)
Transfusion requirements and blood loss[l]			X	X		X	X

Continued on Next Page

Continued

Key: EOS = End of Study Visit; OR = operating room

[a] The Antibody Testing Visit is required. Any de novo (> 0.6 BU) or significantly increased (> 10 BU) results will require confirmatory blood assessments an additional 7 to 14 days later, which is to include the procedures identified here with data recorded as an unscheduled visit.
[b] The End of Study Visit also applies to subjects who withdraw or discontinue prematurely.
[c] If the subject is discharged from surgical facility on the day of the procedure, he should return to the site on Day 1 to perform the postoperative hemostatic efficacy assessment (Day 1 assessment) and the overall peri-operative assessment. In this case, physical examination, vital signs, laboratory assessments, adverse events, and concomitant medications/non-drug therapies must also be assessed. If the subject is discharged from surgical facility after Day 1 but prior to the overall peri-operative assessment, he should return to the site for that assessment as well as the required physical examination, vital signs, laboratory assessments, adverse events, and concomitant medications assessments.
[d] May also be collected as an unscheduled visit.
[e] Occurs prior to any study-specific procedures; as per Section 12.5, includes hemophilia history, bleeding episode history, history of aPCC or rFVIIA usage for 6 months prior to screening.
[f] Preoperative prediction of expected blood loss for a subject with severe hemophilia A with inhibitors and a comparable healthy individual with the same demographic characteristics will be estimated and documented as per Section 11.2.1. This could also be performed days/weeks before the surgery, during the screening period.
[g] Perform physical examination (see Section 12.6) on Days 1, 2, 3, and 7 post surgery (if a subject remains admitted).
[h] For laboratory assessments, see Table 10.
[i] Within 30 minutes pre-dose and 30 ±5 minutes post-dose for FVIII activity.
[j] Blood draws for FVIII activity determination (see Section 11.3) and hematology should be performed coincident with an early morning dose to the greatest extent possible. Samples for laboratory testing (hematology and clinical chemistry) will be taken daily until GHEA 3-Visit from Day 1 through 7 post-surgery and then subsequently once weekly.
[k] Vital signs (see Section 12.8) will include body temperature, pulse rate, blood pressure, respiratory rate. Blood pressure will be measured when subjects are in the supine position. Height and weight will be measured once at Screening. Vital signs will be measured generally at 30 minutes before and 30 ± 5 minutes after each administration of IP. In addition it needs to be measured at Screening, on Days 1, 2, 3 and 7 post surgery (if a subject remains admitted), at the AntibodyTestingVisit and the End of study Visit.
[l] Record blood loss on a daily basis and at drain removal; record blood product usage, whole blood, red blood cells, platelets and plasma

20.4 Clinical Laboratory Assessments

Table 10
Clinical Laboratory Assessments

Period		**Screening**	**Preoperative**	**Intraoperative**	**Postoperative**		**End of Study**	**Laboratory Assessments for Unrelated/Surgical Site Bleeding Episodes During the Postoperative Period (see Section 11.2.5)[c]**
Visit		**Screening**	**Preoperative procedures**	**Intraoperative procedures**	**Postoperative: Daily procedures**	**Antibody Testing Visit[a]**	**End of Study Visit[b]**	
Time point		**Up to 45 days prior to Day 0**	**Day 0 ~60 to 120 minutes prior to surgery**	**Day 0 During surgery**	**Day 1 and daily thereafter until GHEA3**	**7-14 days after last perioperative treatment dose of BAX 802**	**42 ± 7 days after last perioperative treatment dose of BAX 802**	
FVIII activity (clotting *and* chromogenic assay at central laboratory; clotting assay at local laboratory)	Citrated plasma	C	L and C within 30 minutes before loading dose, then 30 ±5 minutes after loading dose[d]	Optional sampling, as deemed necessary: L and C Also, if subject has excessive or unexplained bleeding	L and C[e]		L and C	Optional sampling, as deemed necessary: L and C
PT and aPTT	Citrated plasma	C and L						
Chemistry[f]	Serum	C	L and C	(L)	L Daily Days 1 to 7	C (L)	C (L)	

Table 10
Clinical Laboratory Assessments

Period		Screening	Preoperative	Intraoperative	Postoperative		End of Study	Laboratory Assessments for Unrelated/Surgical Site Bleeding Episodes During the Postoperative Period (see Section 11.2.5)[c]
Visit		**Screening**	**Preoperative procedures**	**Intraoperative procedures**	**Postoperative: Daily procedures**	**Antibody Testing Visit[a]**	**End of Study Visit[b]**	
Time point		**Up to 45 days prior to Day 0**	**Day 0 ~60 to 120 minutes prior to surgery**	**Day 0 During surgery**	**Day 1 and daily thereafter until GHEA3**	**7-14 days after last perioperative treatment dose of BAX 802**	**42 ± 7 days after last perioperative treatment dose of BAX 802**	
Hematology	Whole blood	C[g]	L[h]	(L)	L Daily Days 1 to 7	C (L)	C (L)	
Urinalysis	Urine	C				C	C	
Viral serology[i]	Serum[j]	C						
[redacted]	Citrated plasma	C[g]				C	C	
Anti-BHK binding Antibody titers	Citrated plasma	C				C	C	

Continued on Next Page

Continued

Key: C = central laboratory; EOS = End of Study Visit; L = local laboratory; (L) = local testing optional, to aid in clinical management of patients.

[a] The Antibody Testing Visit is required. Any de novo (> 0.6 BU) or significantly increased (> 10 BU) results will require confirmatory blood assessments an additional 7 to 14 days later, which is to include the procedures identified here with data recorded as an unscheduled visit.
[b] The End of Study Visit also applies to subjects who withdraw or discontinue prematurely.
[c] May also be collected as an unscheduled visit.
[d] It is recommended that the surgery starts after FVIII levels have achieved target levels. If FVIII activity post loading dose is close to the target level, a supplement dose of BAX 802 should be administered without further delaying the surgery. If FVIII activity post loading dose is not close to the target level, a supplement dose of BAX 802 should be administered and surgery delayed until FVIII levels have achieved target levels or are in close range.
[e] FVIII activity should be monitored postoperatively as per instructions in Table 5 and Section 8.7.3.3.3.
[f] Sodium, potassium, chloride, bicarbonate, protein, albumin, ALT, AST, total bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, and glucose.
[g] Hematology and antibody testing should be performed during screening at least 2 weeks before the planned surgery day as hematocrit and anti-pFVIII inhibitor titer values are required for loading dose calculation.
[h] Hematology, without differential but including platelets.
[i] HIV-1 and HIV-2 antibody, HAV (IgM and total antibodies), HBsAg, HBsAb, HBcAb, HCV Ab, and parvovirus B19 (IgM and IgG antibodies). CD4 for HIV positive patients and HCV-RNA or HIV-RNA for confirmatory testing of HIV or HCV positive results, respectively.
[j] Citrated plasma for HCV-RNA or HIV-RNA confirmatory testing.

20.5 Global Efficacy Assessments Scores

Table 11
Combinations of Individual Efficacy Assessments (GHEA1, GHEA2, and GHEA3) and GHEA Score

Individual Assessment Scores (GHEA1, GHEA2, and GHEA3)	GHEA
3 3 3	Excellent
3 3 2	Excellent
3 2 2	Excellent
3 3 1	Good
3 2 1	Good
3 1 1	Good
2 2 2	Good
2 2 1	Good
2 1 1	Fair
1 1 1	Fair
3 3 0	None
3 2 0	None
3 1 0	None
3 0 0	None
2 2 0	None
2 1 0	None
2 0 0	None
1 1 0	None
1 0 0	None
0 0 0	None

20.6 Definitions

20.6.1 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.

20.6.2 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 central nervous system, gastrointestinal, and abdominal hemorrhages see the Guidelines for the management of hemophilia from the WFH.[5,20]

21. REFERENCES

1. Coppola A, Di Capua M, Di Minno MND, et al. Treatment of hemophilia: A review of current advances and ongoing issues. *J Blood Med*. 2010;1:183-195.

2. Janbain M, Leissinger CA, Kruse-Jarres R. Acquired hemophilia A: emerging treatment options. *J Blood Med*. 2015;6:143-150.

3. Mansouritorghabeh H. Clinical and laboratory approaches to hemophilia A. *Iran J Med Sci*. 2015;40(3):194-205.

4. Berntorp E, Shapiro A, Astermark J, et al. Inhibitor treatment in haemophilias A and B: summary statement for the 2006 international consensus conference. *Haemophilia*. 2006;12 Suppl 6:1-7.

5. World Federation of Hemophilia Treatment Guidelines Working Group. Guidelines for the management of hemophilia 2nd Edition. Guidelines for the management of hemophilia 2nd Edition; 2012:80. Web Link: http://www1.wfh.org/publication/files/pdf-1472.pdf

6. Santagostino E, Escobar M, Ozelo M, et al. Recombinant activated factor VII in the treatment of bleeds and for the prevention of surgery-related bleeding in congenital haemophilia with inhibitors. *Blood Rev*. 2015;29 Suppl 1:S9-S18.

7. Valentino LA, Cooper DL, Goldstein B. Surgical experience with rFVIIa (NovoSeven) in congenital haemophilia A and B patients with inhibitors to factors VIII or IX. Haemophilia 589. Vol. 17. Surgical experience with rFVIIa (NovoSeven) in congenital haemophilia A and B patients with inhibitors to factors VIII or IX; 2011:11-579. Web Link: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2010.02460.x/epdf

8. Kempton CL, White GC, II. How we treat a hemophilia A patient with a factor VIII inhibitor. *Blood*. 2009;113(1):11-17.

9. Kasper CK. Effect of prothrombin complex concentrates on factor VIII inhibitor levels. *Blood*. 1979;54:1358-1368.

10. Young G, Sørensen B, Dargaud Y, Negrier C, Brummel-Ziedins K, Key NS. Thrombin generation and whole blood viscoelastic assays in the management of hemophilia: current state-of-art and future perspectives. *Blood*. 2013;121(11):1944-1950.

11. Kempton CL, Abshire TC, Deveras RA, et al. Pharmacokinetics and safety of OBI-1, a recombinant B domain-deleted porcine factor VIII, in subjects with haemophilia A. *Haemophilia*. 2012;18(5):798-804.

12. Mahlangu JN, Andreeva TA, Macfarlane DE, Walsh C, Key NS. Recombinant B-domain-deleted porcine sequence factor VIII (r-pFVIII) for the treatment of bleeding in patients with congenital haemophilia A and inhibitors. *Haemophilia*. 2017;23(1):33-41.

13. Kruse-Jarres R, St Louis J, Greist A, et al. Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A. *Haemophilia*. 2015;21(2):162-170.

14. Brettler DB, Forsberg AD, Levine PH, et al. The use of porcine factor VIII concentrate (Hyate:C) in the treatment of patients with inhibitor antibodies to factor VIII. A multicenter US experience. *Arch Intern Med*. 1989;149(6):1381-1385.

15. Hay CRM, Lozier JN, Lee CA, et al. Safety profile of porcine factor VIII and its use as hospital and home-therapy for patients with haemophilia-A and inhibitors: the results of an international survey. *Thromb Haemost*. 1996;75(1):25-29.

16. Baxter Healthcare Corporation. Package Insert: OBIZUR [antihemophilic factor (recombinant), porcine sequence] lyophilized powder for solution for intravenous injection.;2014. Web Link: https://www.baxter.com/assets/downloads/obizur_pI.pdf

17. Lee CA. The evidence behind inhibitor treatment with porcine factor VIII. *Pathophysiol Haemost Thromb*. 2002;32 Suppl 1:5-8.

18. Kasper C. Diagnosis and Management of Inhibitors to Factors VIII and IX - An Introductory Discussion for Physicians. Vol. 34. Diagnosis and Management of Inhibitors to Factors VIII and IX - An Introductory Discussion for Physicians: World Federation of Hemophilia (WFH); 2004:22. Web Link: http://www1.wfh.org/publications/files/pdf-1178.pdf

19. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, ed. Evaluation of Chemotherapeutic Agents. New York: Columbia University Press; 1949:191-205.

20. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: Communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(22):1935-1939.

22. SUMMARY OF CHANGES

Protocol 241502: Amendment 6, 2017 DEC 14

Replaces: Amendment 4, 2017 JUN 28

In this section, changes from the previous version of the Protocol Amendment 4, dated 2017 JUN 28, are described and their rationale is given.

1. *Throughout the document*
   Description of Change: Minor editorial changes to align with most current protocol template version, to update the list of abbreviations, administrative changes to the study team, and for improved clarity and consistency.
   Purpose of Change: For consistency with the current Baxalta protocol template, and to improve clarity and consistency (note: minor edits and deletions that do not substantively change the protocol or are administrative in nature are not individually listed below). Note that changes that are found in the synopsis and more than one section in the body may have minor differences in wording; the common substantive changes are presented here.

2. *Throughout the document*
   Description of Change: the utilization and the definition of the term "blood products" was harmonized throughout the protocol.
   Purpose of Change: For greater clarity and consistency

3. *Section 2 "SAE Reporting"*
   Description of Change: the standard protocol template text describing the SAE reporting process was made more specific.
   Purpose of Change: For greater clarity and to prevent any ambiguity

4. *Synopsis; Section 8.3 "Duration of Study Period(s) and Subject Participation"*
   Description of Change: the initiation of the trial and the total planned duration of the trial were updated.
   Purpose of Change: Information update

5. *Synopsis; Section 8.3 "Duration of Study Period(s) and Subject Participation", Section 10.4.4 "End of Study Visit"*
   Section 10.7 "Subject Completion/Discontinuation", Table 9 and Table 10
   Description of Change: The timing of the End of Study Visit for each patient was harmonized throughout the study protocol.
   Purpose of Change: For greater clarity and to prevent any ambiguity

6. *Synopsis, Section 8.4.1 Primary Outcome Measures,*
   Section 10.4.1 "GHEA3 Visit" and Table 8 Summary of Required Procedures
   Description of Change: Information was added to the description of the GHEA 3 assessment
   Purpose of Change: For greater clarity and to prevent any ambiguity

7. *Synopsis, Section 8.4.1 Primary Outcome Measures and*
   Table 8 "Summary of Required Procedures"
   Description of Change: The requirement to return to the site for a GHEA 2 assessment in case of a discharge within 24 hours after the surgery was introduced.
   Purpose of Change: To ensure the GHEA 2 data is collected for each patient

8. *Synopsis and Section 13.4.1 Primary Outcome Measure*
   Description of Change: Deleted "If discharge is delayed for a reason other than surgery related bleeding (e.g., pneumonia), an assessment at 24 to 78 hours after last perioperative treatment dose of BAX 802 will ensure that the overall perioperative assessment is completed close to the last administered study drug dose. "
   Purpose of Change: To align with the revised definition of the GHEA 3 visit

9. *8.2.2 "Dose Selection Rationale",*
   8.7.3.3 "Dosing Schedule and Requirements" and
   Table 5 "Dosing for Perioperative Management"
   Description of Change: The units in which BAX 802 loading dose and anti-pFVIII inhibitor titer are expressed were added
   Purpose of Change: For greater clarity

10. *Section 8.3 "Duration of Study Period(s) and Subject Participation"*
    Description of Change: The following sentence was added: "A subject is considered enrolled by signing the Informed Consent Form."
    Purpose of Change: For consistency with the information in the Synopsis

11. *Table 5 "Dosing for Perioperative Management" and Table 8 "Summary of Required Procedures"*
    Description of Change: added that the recommended doses are for subjects for whom the "GHEA3 [was] not yet performed"
    Purpose of Change: For greater clarity and to prevent any ambiguity

12. *Section 8.7.3.3.2 "Preoperative and Loading Dose"; Section 8.7.3.3.3 "Postoperative Dosing" and Section 10.6 "Rescue Medication"*
    Description of Change: the following warning was added, "Although peak levels above 200% may be achieved, it is recommended that the plasma levels of FVIII are not sustained above 200% of normal."
    Purpose of Change: For clarification of dosing, as recommended by the DSMB.

13. *Section 8.7.3.3.3 "Postoperative Dosing" and Section 10.6 "Rescue Medication"*
    Description of Change: advice was added to increase frequency and /or dose of study drug to achieve the recommended FVIII trough levels
    Purpose of Change: For greater clarity and to address DSMB concern of underdosing with BAX 802 in the postoperative period.

14. *Section 8.7.3.3.3 "Postoperative Dosing"*
    Description of Change: recommendation was added on how to proceed with dose adjustment when dosing intervals are to frequent to obtain post-dose FVIII level results prior to next dosing.
    Purpose of Change: For greater clarity and to address DSMB concern of underdosing with BAX 802 in the postoperative period.

15. *Section 8.7.3.3.4 "Dosing for Unrelated/Surgical Site Bleeding Episodes during the Postoperative Period"*
    Description of Change: re-phrased the information regarding follow-up treatment with SOC product if subject cannot continue receiving the IP at the study site, or subject cannot travel to the site.
    Purpose of Change: For greater clarity.

16. *Section 10.4* "*Study Periods" and Section 20.1 Procedures per Study Period*
    Description of Change: the description of the End of Study Visit previously part of Section 10.4.1 was made a new distinct *Section 10.4.4* "*End of Study Visit"*
    Purpose of Change: For greater clarity

17. *Section 10.4* "*Study Periods", Section 11.2.5* "*Hemostatic Efficacy Rating for Treatment of Unrelated/Surgical Site Bleeding Episodes"*
Section 11.3 "*Factor VIII Activity",*
Section 20.1 Procedures per Study Period, Table 9 and Table 10
Description of Change: the Discharge Visit Section was renamed "GHEA3 Visit and the timing of this visit was re-defined.
Purpose of Change: For greater clarity

18. *Section 10.4.4* "*End of Study Visit"*
Description of Change: Information was added: "The End of Study Visit should be performed in ALL subjects who have received at least a dose of BAX 802 during Study 241502. This applies also to subjects who receive dose(s) of BAX 802 and do not undergo surgery and withdraw from the study AND to subjects who receive any rescue medications and subsequently withdraw from the study. "
Purpose of Change: For greater clarity

19. *Section 10.5 "Medication and Non-Drug Therapies*
Description of Change: precision was added regarding the period during which the listed non-permitted medications are not allowed.
Purpose of Change: For greater clarity and to prevent any ambiguity

20. *Section 10.6 "Rescue Medications"*
Description of Change: additional precisions were added to the recommendation for when the use of rescue medication should be considered by the investigator.
Purpose of Change: For greater clarity and to address DSMB concern of underdosing with BAX 802 in the postoperative period.

21. *Section 10.6 "Rescue Medications" and Table 8, Section 3 and Section 4*
Description of Change: the requirement for patients who switched to rescue medication to attend the End of Study Visit was added in this section.
Purpose of Change: To align with the definition of End of Study Visit in Section 10.4.4

22. *Section 11.2.3 Bleeding episodes", and*
Section 11.2.5 "Hemostatic Efficacy Rating for Treatment of Unrelated/Surgical Site Bleeding Episodes"
Description of Change: the definition of "surgical site bleeding episodes" was simplified
Purpose of Change: For greater clarity

23. *Section 12.7 Clinical Laboratory Parameters* and *Table 10*
Description of Change: Duplicated information was deleted and a reference to the sample sample collection schedule added.
Purpose of Change: For greater clarity

24. *Section 12.8 Vital Signs* and *Table 9*
Description of Change: Additional information was inserted regarding vital sign assessment schedule.
Purpose of Change: For greater clarity

25. *Section 20.1 Procedures per Study Period*
Description of Change: Table 8 was revised to incorporate the changes made to the required procedures described in the protocol
Purpose of Change: For consistency with the information in the study protocol body.

26. Section 20.3 "Schedule of Study Procedurals Assessments"
Description of Change: Table 9 was updated to incorporate the revisions related to the schedule of study procedures and assessments
Purpose of Change: For consistency with the information in the study protocol body.

27. Section 20.3 "Schedule of Study Procedurals Assessments"
Description of Change: procedures and laboratory assessments for unrelated/surgical site bleeding episodes during the postoperative period were presented in a new layout in Table 9 and Table 10, respectively.
Purpose of Change: For greater clarity.

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: BAX 802

STUDY TITLE: A Phase 3, Multicenter, Single-arm, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX 802) in Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures

PROTOCOL IDENTIFIER: 241502

CLINICAL TRIAL PHASE 3

AMENDMENT 6: 2017 DEC 14

Replaces: AMENDMENT 4: 2017 JUN 28

OTHER ID(s)
NCT Number: NCT02895945
EudraCT Number: 2015-005521-39
IND NUMBER: BB-IND 014798

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 Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: BAX 802

STUDY TITLE: A Phase 3, Multicenter, Single-arm, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX 802) in Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures

PROTOCOL IDENTIFIER: 241502

CLINICAL TRIAL PHASE 3

AMENDMENT 6: 2017 DEC 14

Replaces: AMENDMENT 4: 2017 JUN 28

OTHER ID(s)
NCT Number: NCT02895945
EudraCT Number: 2015-005521-39
IND NUMBER: BB-IND 014798

By signing below, the Investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD
[redacted], Clinical Programs and Therapeutic Area Head
Baxalta Innovations GmbH