STATISTICAL ANALYSIS PLAN

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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

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BAX 802
PHASE 3

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

Study Sponsor(s):	**Baxalta US Inc.** 300 Shire Way Lexington, MA 02421, UNITED STATES	**Baxalta Innovations GmbH** Industriestrasse 67 A-1221 Vienna, AUSTRIA

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REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	2018 OCT 12	New Document
2.0	2021 MAR 22	Updated for consistency with protocol, removed PPAS, added DAS, added de novo and anamnestic reactions, changed analysis from surgery-based to subject-based, updated exposure section, removed 'first surgery' analyses, modified section 12, added summaries for concomitant medications and rescue medications, and other minor edits.
3.0	2021 APR 20	Restored PPAS and corresponding analyses. Updated the handling of subjects that received a bypassing agent regardless of the GHEA assessment for analyses performed with the DAS.

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ABBREVIATIONS

AE	adverse event
BHK	baby hamster kidney
BU	Bethesda units
CHA	Congenital Hemophilia A
CTMS	Clinical Trial Management System
DAS	Dosed in preparation for surgery Analysis Set
eCRF	electronic case report form
FAS	Full Analysis Set
FVIII	factor eight
GHEA	Global Hemostatic Efficacy Assessment
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.
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 the operating surgeon. In cases where the rating differs, the rating of the Investigator will be used.
hFVIII	human factor eight
IgG	immunoglobulin G
IgM	immunoglobulin M
IP	investigational product
MedDRA	Medical Dictionary for Regulatory Activities
pFVIII	porcine factor eight
PPAS	Per-protocol Analysis Set
SAP	statistical analysis plan
SAS	Safety Analysis Set
SD	standard deviation
SOC	system organ class
TEAE	treatment emergent adverse event
WHO-DD	World Health Organization - Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy and safety data as described in the protocol for Study 241502. Specifications for tables, figures, and listings are contained in a separate Output Templates document.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

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

2.1.2 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-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.

2.1.3 Exploratory Objectives

The exploratory objectives of the study are:

- [redacted]

2.2 Outcome Measures

2.2.1 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. Refer to Section 6.1 for details on what the GHEA is comprised of.

Hemostatic efficacy success is defined as "excellent" or "good" outcome for ≥ 70% of hemostatic efficacy assessments.

2.2.2 Secondary Outcome Measures

2.2.2.1 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 comparably 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.

2.2.2.2 Safety

1. Development of, and changes to, the titer of inhibitory and binding antibodies (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 investigational product (IP)-related AEs.
7. Incidence of clinically significant changes in vital signs and routine laboratory parameters (hematology, clinical chemistry).

2.2.3 Exploratory Outcome Measures

[redacted]

3. STUDY DESIGN

3.1 General Description

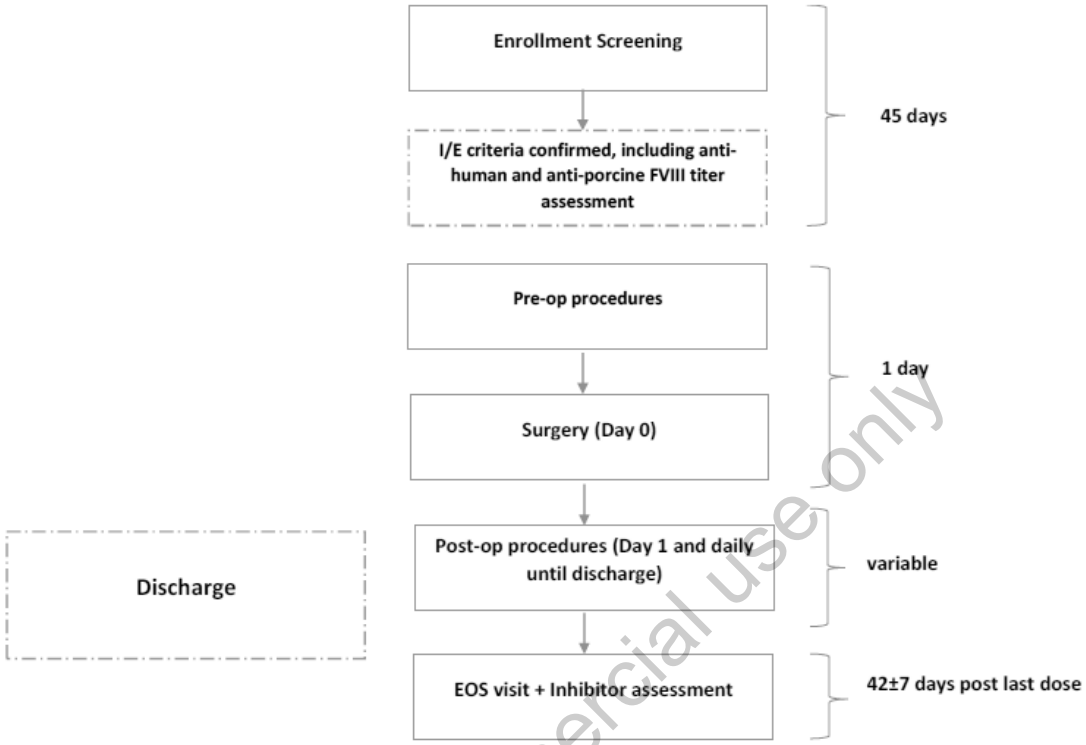
This study is a Phase 3, prospective, single-arm, open-label, uncontrolled, multicenter study to evaluate the efficacy and safety of BAX 802 in at least 12 procedures in 12 evaluable male subjects ≥ 12 to ≤ 75 years old with CHA with inhibitors to hFVIII who are undergoing major or minor surgical, dental 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 non-operative invasive procedures, and at least 3 adult subjects with screening anti-hFVIII titers of ≥ 5 Bethesda units (BU) for inhibitors to hFVIII will be enrolled in the study. At least 2 adolescents (≥ 12 to < 18 years old) will be enrolled in the study.

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 measures. 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 for the next surgery. 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.

The study will be divided into 5 periods: Screening, Preoperative, Intraoperative, Postoperative, and End of Study. A study flowchart detailing the visit schedule is provided in Figure 1.

Figure 1 Study Flow Chart



EOS = End of Study. FVIII = Factor VIII. I/E: Inclusion/Exclusion.

3.2 Randomization and Blinding

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

3.3 Sample Size and Power Considerations

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 to be 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.

4. STATISTICAL ANALYSIS SETS

4.1 Screened Analysis Set

The Screened Analysis Set will consist of all subjects who have signed informed consent as obtained from the *Screening* electronic case report form (eCRF).

4.2 Safety Analysis Set (SAS)

The Safety Analysis Set (SAS) will be comprised of all subjects in the Screened Analysis Set who received any amount of BAX 802. The SAS will consist of all subjects in the Screened Analysis Set for which any amount of IP was administered as obtained from the *BAX 802 Administration* eCRF. Should it happen that a subject is dosed with BAX 802, but do not undergo any procedure during this study, this subject will be included in SAS.

4.3 Full Analysis Set (FAS)

The Full Analysis Set (FAS) will be comprised of all subjects with at least 1 available hemostatic efficacy assessment. The FAS will consist of subjects in the SAS and for whom at least 1 hemostatic efficacy assessment as obtained from the *Efficacy Assessment Scale* eCRF is available.

4.4 Dosed in preparation for surgery Analysis Set (DAS)

The Dosed in preparation for surgery Analysis Set (DAS) will be comprised of all subjects who are dosed in preparation for surgery.

4.5 Per-protocol Analysis Set (PPAS)

The Per-protocol Analysis Set (PPAS) will consist of all subjects included the SAS with evaluable ratings for all 3 perioperative hemostatic efficacy assessments as obtained from the *Efficacy Assessment Scale* eCRF is available, have met all study entry criteria, and had no major protocol violations that may have an impact on the hemostatic efficacy assessments.

All protocol deviations to be considered for the PPAS will be obtained from the IQVIA managed Clinical Trial Management System (CTMS). Prior to performing any analysis as set out in this SAP, all major deviations entered into CTMS will be reviewed by the team for impact to the assessment of hemostatic efficacy. It will be documented if the major deviation resulted in the subject's exclusion from the PPAS or not. It should therefore be noted that not all major protocol deviations will result in an exclusion from the PPAS. As protocol deviations from CTMS will be used to determine eligibility for the PPAS all efforts should be made to ensure that the deviations in CTMS is complete and

finalized prior to team review. The exclusions must be agreed upon by representatives of Biostatistics and Medical from both IQVIA and Shire, and signed off before performing any analysis as set out in this SAP.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

A listing of all Screen Failures will be presented.

The number of subjects included and excluded from each defined analysis set (refer to Section 4) will be summarized by surgical classification (major or minor) and overall, except for the Screened Analysis Set, which will be summarized only overall. A listing including the reason for exclusion from each defined analysis set will also be presented.

The number and percentage of subjects completed and prematurely discontinued the study will be presented for each surgical classification (major or minor) and overall for the SAS. Reasons for premature discontinuation as recorded on the *Completion/Termination* eCRF will be summarized (number and percentage) by surgical classification (major or minor) and overall for the SAS. All subjects who prematurely discontinued the study will be listed including discontinuation reason for the Screened Analysis Set. A disposition flowchart presenting the number of subjects screened, dosed, completed and discontinued will further be presented by surgical classification (major or minor) and overall for the Screened Analysis Set.

The number of subjects screened, treated and completed will be tabulated by site for the Screened Analysis Set. In addition, the duration of enrollment, in days, will be summarized for each site, and overall. Duration of enrollment will be calculated as (last date of contact for any subject/surgery at that site - the first date of informed consent for any subject/surgery at that site + 1).

A listing of subjects that deviated from the inclusion/exclusion criteria will be presented for the Screened Analysis Set.

5.2 Protocol Deviations

Protocol deviations will be recorded in the CTMS and will be classified as major or minor. A biostatistical review of the protocol deviations will be performed prior to any analysis presenting protocol deviations.

Major/minor protocol deviations will be summarized by category and site for each surgical classification (major or minor) and overall, for the SAS. Protocol deviations will be listed for the SAS.

Deviation categories will be included as part of the CTMS protocol deviations log and may include any of the following categories:

- Informed consent.
- Eligibility and entry criteria.
- Concomitant medication criteria.
- Laboratory assessment criteria.
- Study procedures criteria.
- Serious AE criteria.
- Visit schedule criteria.
- Investigational product compliance.
- Efficacy criteria.
- Administrative criteria.
- Source document criteria.
- Regulatory or ethics approval criteria.
- Other criteria.

5.3 Demographics, Screening Characteristics and Surgery

Descriptive summaries of demographics, screening characteristics, and surgery to be performed will be presented by surgical classification (major or minor) and overall for the SAS, FAS, DAS, and PPAS. Demographics, screening characteristics, and surgery to be performed will be listed for the SAS.

Demographic variables will include age, age category, sex, race, and ethnicity as reported on the *Demography* eCRF. For summary purposes, age will be categorized as follows:

- Age ≥ 12 to < 18.
- Age ≥ 18 to ≤ 75.

Screening characteristics to be summarized and listed will be the corresponding value to which the subject was enrolled onto the study. These values will include height and weight as reported on the *Vital Signs* eCRF, Karnofsky performance score as reported on the *Karnofsky Index* eCRF as well as select Screening laboratory results as obtained from

the central laboratory. The select Screening laboratory results will include FVIII activity, inhibitors to hFVIII and pFVIII, anti-hFVIII and anti-pFVIII binding antibodies (IgG and IgM), anti-BHK antibodies, alanine aminotransferase, prothrombin international normalized ratio, prothrombin time, activated partial thromboplastin time, serum creatinine, hemoglobin, platelet counts, human immunodeficiency virus status, and hepatitis C virus results.

Body mass index will be derived (accurate to 1 decimal place) from eCRF recorded height and weight as follows for presentation in summaries and listings:

$$BMI(kg/m^2) = \frac{weight(kg)}{height(m)^2}$$

Surgery information as obtained from the *Planned Surgery* eCRF will include the surgery name and information on the site of the surgery. Surgery information will be coded with the version of the Medical Dictionary for Regulatory Activities (MedDRA) as specified in the data management coding guidelines.

5.4 Medical and Surgical History

Medical and surgical histories as collected on the *Medical History* eCRF will be summarized by system, surgical classification (major or minor) and overall for the SAS. A listing presenting medical and surgical histories will be presented for the SAS.

Data on medical and surgical histories will not be coded.

5.5 Bleeding History

Information on bleeding history will be obtained from the *Bleeding History* eCRF.

No summaries will be presented on bleeding histories. Bleeding histories will be listed for the SAS.

5.6 Prior Hemophilia Treatment

All data on prior hemophilia treatments will be obtained from the *Prior Hemophilia Treatment* eCRF. Prior hemophilia treatment will be coded using the version of the World Health Organization – Drug Dictionary (WHO-DD) as specified in the data management coding guidelines.

No summaries will be presented for prior hemophilia treatment. Prior hemophilia treatment information will be listed for the SAS.

5.7 Prior and Concomitant Medications, Therapies and Procedures

All data on medications, therapies and procedures will be obtained from the *Concomitant Medications/Non-Drug Therapy* eCRF. Medications will be coded using the WHO Dictionary Global version September 2020 B3. Therapies and procedures will not be coded.

Medications, therapies and procedures will be assigned as prior or concomitant using the following rules:

- Prior: if the medication, therapy or procedure stopped prior to first BAX 802 administration.
- Concomitant: if the medication, therapy or procedure
    - started after first BAX 802 administration; or
    - started before the first BAX 802 administration and ended after first BAX 802 administration or is still ongoing.
- Unknown: if missing dates do not allow for assignments on above rules.

No imputation on dates for medications, therapies or procedures will be performed. Where possible, the assignment of prior and concomitant will still be done if it is clear from the partial date to which category the medication, therapy or procedure belongs.

A medication will be considered a rescue medication if indicated as “Rescue for perioperative management” in the eCRF.

Concomitant medications, excluding rescue medications and concomitant rescue medications will be summarized by therapeutic class, preferred name, and surgical classification (major or minor) and overall for the SAS. No summaries will be presented on therapies, procedures, or prior medications. Medication, therapy and procedure data will be listed for the SAS. Separate listings will be produced for rescue medications on the SAS.

5.8 Exposure to BAX 802

Information on BAX 802 administration will be obtained from the *BAX 802 Administration* eCRF for surgery-related infusions and [redacted]

The following derivations based on eCRF reported data will be performed:

- Infusions will be assigned to an operative period as follows:
    - Preoperative if infusion information is entered at the preoperative visit. Infusion information entered at an unscheduled visit will be assumed to be preoperative if the date of the infusion is before the date of surgery.
    - Intraoperative if infusion information is entered at the intraoperative visit or if the bleed for which infusion was given occurred intraoperatively.
    - Postoperatively if infusion information is entered at any postoperative visit or the bleed for which infusion was given occurred postoperatively. Infusion information entered at an unscheduled visit will be assumed to be postoperative if the date of the infusion is on or after the date of surgery.
- Body-weight adjusted dose will be derived using the amount infused (IU) and the last available body-weight (kg) prior to the infusion as follows:

$$Body\ weight\ adjusted\ dose(IU/kg) = \frac{Amount\ infused\ (IU)}{Body - weight(kg)}$$

- Total dose for each operative period (as defined above) and overall will be determined as the sum of all amounts infused within that period.
- Total dose for surgery-related infusions for each operative period (as defined above) and overall will be determined as the sum of all amounts infused within that period.
- Total dose for bleed-related infusions for each operative period (as defined above) and overall will be determined as the sum of all amounts infused within that period.
- The number of surgery-related infusions for each operative period (as defined above) and overall will be determined as the count of infusions within that period.
- The number of bleed-related infusions for each operative period (as defined above) and overall will be determined as follows:
    - $Bleed\ Duration \times 1$ if treatment frequency is indicated as “QD”.
    - $Bleed\ Duration \times 2$ if treatment frequency is indicated as “BID”.
    - $Bleed\ Duration \times 3$ if treatment frequency is indicated as “TID”.
    - $Bleed\ Duration \times 4$ if treatment frequency is indicated as “QID”.
    - 1 if treatment frequency is indicated as “QS” or “Once”.
    - Undeterminable if frequency is indicated as “PRN”.
    - Other frequencies will be defined on a case-by-case basis during the analysis.

where $Bleed\ Duration = Bleed\ Resolution\ Date - Bleed\ Start\ Date + 1$.

- Preoperative and intraoperative periods will be for a duration of 1 day.
- The number of postoperative days will be determined from date of discharge as obtained from the *Discharge* eCRF as:

$$Postoperative\ Days = Date\ of\ Discharge - Date\ of\ Surgery + 1$$

- The average dose (IU/kg) per infusion will be derived as:

$$Average\ Dose(IU/kg) per\ infusion = \frac{Total\ Dose\ Infused\ (IU/kg)}{Number\ of\ Infusions}$$

- The average dose (IU/kg) per day in the operative period will be derived as:

$$Average\ Dose(IU/kg)\ per\ infusion = \frac{Total\ Dose\ Infused\ (IU/kg)\ in\ Operative\ Period}{Number\ of\ Days\ in\ Operative\ Period}$$

Information on BAX 802 administration and exposure as reported on the eCRF and derived will be summarized and listed for the SAS.

5.9 Compliance

Compliance to BAX 802 administration will be presented relative to the following planned doses:

- FVIII maintenance plan as entered on the *Approved FVIII Maintenance Plan* eCRF at the time of the infusion.
- Protocol planned dose as derived below.

The protocol planned dose will be derived as follows:

<u>Loading Dose for BAX 802 (administered approximately 1 to 2 hours prior to surgery)</u>:

- Major surgery: $[80 \times body\ weight\ (kg)]U + \left[body\ weight\ (kg) \times 40\left(1 - \left[\frac{HCT\%}{100}\right]\right) \times anti - pFVIII\ inhibitor\ titer\ (BU/mL)\right]U$

- Minor surgery: $[50 \times body\ weight\ (kg)]U + \left[body\ weight\ (kg) \times 40\left(1 - \left[\frac{HCT\%}{100}\right]\right) \times anti - pFVIII\ inhibitor\ titer\ (BU/mL)\right]U$

where HCT% represents hematocrit results.

Screening anti-pFVIII and hematocrit results will be used in the above calculations.

Subsequent Doses:

$$Recommended\ Dose(U) = \frac{body\ weight\ (kg) \times [Target\ FVIII\ Level - FVIII(\%)]}{1.2}$$

where the FVIII (%) result is the most recent result available prior to the infusion. For the purposes of dose calculations, any FVIII result below the limit of quantification will be set to 0%.

The target level to be used in the above calculation is set out in Table 1.

Table 1 Target FVIII Level (% of normal)

Timepoint	Major Surgery	Minor Surgery
Postoperative up to 72 hours (if not yet discharged and GHEA3 not yet performed)	80%	50%
Postoperative Day 4 – Day 7 (if not yet discharged and GHEA 3 not yet performed)	50%	30%
After postoperative Day 8 (if not yet discharged and GHEA3 not yet performed)	30%	30%

GHEA3: Assessment of overall perioperative hemostatic efficacy of BAX 802 at discharge or within 24 to 72 hours after last perioperative treatment dose of BAX 802 (whichever is earlier).

The ratio of actual dose to planned dose (either of the two) will be derived as

$$Ratio = \frac{Actual(IU)}{Planned(IU)}$$

Where multiple doses from part of a specific operative period or overall for the summaries the sum of actual (IU) and planned (IU) will be used to determine the above ratio.

The planned dose and the ratio of actual to planned doses will be listed and summarized for each operative period (as defined in Section 5.8) and overall for the SAS.

6. EFFICACY ANALYSES

6.1 Analyses of the Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of surgeries with a "good" or "excellent" response as measured by the GHEA score.

The GHEA score is comprised 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.
- 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 the operating surgeon. In cases where the rating differs, the rating of the Investigator will be used.

The GHEA will be derived as composite of GHEA1, GHEA2 and GHEA3 as set out in the appendices (Section 14.1). Any missing results in GHEA1, GHEA2 or GHEA3 will be handled as described in Section 10.5. For analyses conducted with DAS, if a subject is dosed in preparation for surgery and does not met the required FVIII levels to proceed with surgery with either the initial dose or supplemental dose, the subject will be considered "not successful" for the evaluation of hemostatic efficacy. Further for analyses conducted with DAS, if a subject, for any reason, receives a bypassing agent (FEIBA or NovoSeven) prior to the assessment of GHEA3, the subject will be considered "not successful" for the evaluation of hemostatic efficacy. Individual GHEA scores as well as a combined group of "Excellent" or "Good" will be presented in listing summaries. Hemostatic efficacy success is defined as an "excellent" or "good "outcome for ≥ 70% of hemostatic efficacy assessments.

No hypothesis testing will be performed on the primary efficacy endpoint. Exact 2-sided Clopper-Pearson 95% confidence intervals will be presented for the rate of hemostatic efficacy assessments with a combined result of "Excellent" or "Good".

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.

Note that the number of surgeries is the same as the number of subjects since each subject had only one surgery. 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.

The following SAS® code will be used to obtain the confidence limits.

```
PROC FREQ DATA = <ds>;
        WEIGHT <count>;
        TABLES <result> / binomial (exact cp) cl;
RUN;
```

where <ds> refers to the input dataset, <count> the number of patients with a particular result and <result> the actual result, i.e., "Excellent or Good" vs. "Not Excellent or Good".

All summaries on the primary efficacy endpoint will be presented for the FAS, DAS, and PPAS, and will be listed for the DAS.

6.1.1 Multiplicity Adjustment for the Primary Efficacy Endpoint

No multiplicity adjustments will be performed during the analysis of this study.

6.2 Analyses of Secondary Efficacy Endpoints

6.2.1 Intra- and Postoperative Blood Loss

Information on expected blood loss will be obtained from the *Expected Blood Loss* eCRF and information on actual blood loss will be obtained from the *Actual Blood Loss* eCRF.

Actual blood loss results entered at the intraoperative visit will be assigned as intraoperative, results entered at postoperative Day 0 and Day 1 will be assigned as

postoperative, and all results entered in the eCRF will be assigned to be perioperative. Therefore, results entered at the intraoperative visit will contribute to both intraoperative and perioperative operative periods, and results entered at postoperative Day 0 and Day 1 will contribute to both postoperative and perioperative periods. The total blood loss during each operative period (intraoperative, postoperative or perioperative) will be derived as the sum of all blood loss records for that period.

The ratio of actual blood loss against expected average and maximum blood loss will be derived as

$$Ratio = \frac{Actual}{Expected}$$

where "Expected" refer to either the expected average or expected maximum blood loss as applicable. Should the expected blood loss be 0, the ratio will be presented as "not calculable" in listings and excluded from summaries.

Expected blood loss, actual blood loss and calculated ratios will be summarized and listed for the FAS.

6.2.2 Hemostatic Efficacy of Major Surgeries

Analysis of hemostatic efficacy of major surgeries will be done in conjunction with the primary efficacy endpoint as described in Section 6.1 and will be presented together.

6.2.3 Daily and Total Weight-adjusted Administration of BAX 802

Daily and total weight-adjusted administration of BAX 802 is described in Section 5.8.

6.2.4 Blood Products Transfused

Blood product transfusion information will be obtained from the *Transfusion Requirement* eCRF.

Blood product transfusion information will be summarized and listed for the FAS.

6.3 Analyses of Exploratory Endpoints

[redacted]

[redacted]

7. SAFETY ANALYSIS

The safety analysis will be performed using the SAS. Safety variables include AEs, clinical laboratory variables, and vital signs. For each safety variable, the last value collected before the first dose of IP will be used as baseline for all analyses of that safety variable.

7.1 Adverse Events

AEs as obtained from the *Adverse Event* eCRF will be coded using the version of the MedDRA as specified in the data management coding guidelines.

An AE will be considered as a treatment emergent AE (TEAE) if the AE started during or after first BAX 802 administration. Should the start date be partial, it is expected that an indication is provided on the eCRF on whether the AE started prior to first BAX 802 administration or after. No imputation of dates will therefore be required to determine if an AE occurred during or after first BAX 802 administration.

An overall summary of the number of subjects with TEAEs as well as the number of events will be presented, including the number and percentage of subjects with any TEAEs, serious TEAEs, TEAEs related to BAX 802, serious TEAEs related to BAX 802, TEAEs leading to drug withdrawn, TEAEs leading to study discontinuation, TEAEs leading to death, TEAEs considered an allergic reaction to BAX 802, TEAEs considered to be an occurrence of a thrombotic event, TEAEs related to study procedures, local TEAEs, systemic TEAEs, TEAEs occurring within 24 hours of last BAX 802 administration, and TEAEs related to inhibitors.

The number and percentage of subjects reporting TEAEs, as well as the number of events, in each surgical classification (major or minor) and overall will be tabulated by system organ class (SOC) and preferred term, and by SOC, preferred term, and maximum severity. TEAEs considered related to IP will also be summarized by SOC and preferred term. If more than 1 AE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe and

most related occurrence for the summarization by severity and by relationship to IP. Presentation by SOC and preferred term will be presented by descending incidence. Listings will be presented on all AEs, serious AEs, AEs leading to death, AEs leading to drug withdrawal, AEs leading to study discontinuation, and AEs related to inhibitors.

The number and percentage of subjects with thrombotic events and severe allergic reactions, as well as the number of events, in each surgical classification (major or minor) and overall, will be tabulated. If related to BAX-802, thrombotic events and allergic reaction events are identified on the *Adverse Event* eCRF as assessed by the investigator. Thrombotic events will be identified by the investigator assessment. Severe allergic reactions will be identified by both the investigator assessment and an indication of "Severe" on the eCRF.

The following derivations based on eCRF reported data will be performed:

Relationship of AE:

The AE will be considered related to BAX 802 if relationship is indicated as "Possibly related" or "Probably related" in the eCRF. AEs indicated as "Not related and "Unlikely related" will be summarized as "Not related". Missing relationship results will be presented as "Unknown" in the AE summaries.

Severity of AE:

Severity of AEs will be summarized as reported in the eCRF. Missing results will not be imputed and will be presented as "Unknown" in the AE summaries.

Duration of AE:

The duration of AE will be calculated as:

$$Duration\ (Hours) = AE\ Stop\ Date\ and\ Time - AE\ Start\ Date\ and\ Time$$

if time is available for both the start and stop dates of the AE. The duration will be presented in hours should the result be ≤ 24 hours. If the result is > 24 hours the result will be presented in days as described below.

If time is missing for either the start date or the stop date of the AE, or the duration as calculated above resulted in > 24 hours, then the duration will be presented in days, calculated as follows:

$$Duration\ (Days) = AE\ Stop\ Date - Start\ Date\ + 1$$

If either the start date or stop date is partial or completely missing, no duration will be calculated.

Time since last BAX 802 administration:

Time since last BAX 802 administration will only be presented for TEAEs. The last BAX 802 administration is defined as the administration immediately preceding the start of the AE. The start date of the preceding BAX 802 administration will be used for all calculations.

Time since last BAX 802 administration will be calculated as:

$$Time\ Since\ Admin\ (Hours) = AE\ Start\ Date\ and\ Time - Dose\ Date\ and\ Time$$

if time is available for both the start date of the AE and the time of dosing administration. Time since last administration will be presented in hours should the result be ≤ 24 hours. If the result is > 24 hours the result will be presented in days as described below.

If time is missing from either the start date of the AE or the dose administration, or the time since last administration is > 24 hours, then the result will be presented in days, calculated as follows:

$$Time\ Since\ Admin\ (Days) = AE\ Start\ Date - Dose\ Date + 1$$

Inhibitor related AEs:

Prior to performing any analyses as described in this SAP, AEs will be reviewed by the medical team and all AEs related to inhibitors will be flagged for use in the analyses.

Development of De Novo Obizur Inhibitors:

Development of de novo obizur inhibitors is defined as a post-baseline anti-pFVIII antibody titer ≥0.6 BU/mL after a non-measurable titer at baseline (anti-pFVIII antibody

titer <0.6 BU/mL). Anti-pFVIII antibody titer values will be used to identify de novo obizur inhibitors. The number and percentage of subjects with de novo obizur inhibitors will be tabulated.

Anamnestic Reactions:

An anamnestic reaction is defined as an increase in the inhibitor titer to FVIII (human or porcine) of ≥10 BU/mL. Changes in inhibitor titer to FVIII (human or porcine) values from baseline will be used to identify anamnestic reactions. The number and percentage of subjects with anamnestic reactions will be tabulated by type of inhibitor (human or porcine) and overall.

A listing of anti-pFVIII and anti-hFVIII antibody titer values will be provided including all inhibitor values, changes from baseline, if the anti-pFVIII >0.6 BU/mL (de novo), and if the change from baseline in anti-pFVIII or anti-hFVIII was ≥10 BU/mL (anamnestic reaction).

7.2 Clinical Laboratory Data

Descriptive statistics for clinical laboratory values as obtained from the central laboratory (in standardized units) and changes from baseline as well as shift tables from baseline will be presented by surgical classification (major or minor) and overall.

The following clinical laboratory parameters will be included in analyses:

Hematology	hemoglobin, hematocrit, erythrocytes (i.e., red blood cell count), leukocytes (i.e., white blood cell count), differentials (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils), platelet counts.
Chemistry	sodium, potassium, chloride, bicarbonate, protein, albumin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, glucose.
Urinalysis	pH, protein, ketones, glucose, bilirubin, blood, urobilinogen, specific gravity
Viral Serology	human immunodeficiency virus 1/2 antibody, hepatitis A virus ([IgM] and total antibodies), hepatitis B surface antigen, hepatitis

	B surface antibody, hepatitis B core antibody, hepatitis C virus antibody, parvovirus B19 (IgM and IgG antibodies).
Immunogenicity	anti-pFVIII and hFVIII binding (IgG and IgM) and inhibitory antibodies and anti-BHK binding antibodies.
FVIII Activity	chromogenic and 1-stage clotting.

The only pre-treatment timepoint that will be presented for analyses will be Baseline as defined in Section 10.3.

All laboratory data (including data from local laboratories [as obtained from the eCRF], data at unscheduled visits and data from tests not mentioned above) will be listed.

Any quantitative laboratory measurement reported as "<X", i.e., below the limit of quantification, or ">X", i.e., above the upper limit of quantification will be presented as recorded, i.e., as "<X" or ">X" in listings.

Except for FVIII activity results, results reported as "<X" or ">X" will be summarized as "X". For FVIII activity results reported as "<X" will be summarized as 0 while results reported as ">X" will be summarized as "X".

7.3 Vital Signs

Descriptive statistics for vital signs as obtained from the *Vital Signs* eCRF (e.g., systolic and diastolic blood pressure, body temperature, pulse rate, and respiratory rate) and their changes from baseline as well as shift tables at each post-baseline visit will be presented by surgical classification (major or minor) and overall.

All vital signs data will be listed for the SAS.

Normal ranges to use in determining whether vital sign parameters are low, normal or high are provided in Table 2.

Table 2 Vital Signs Normal Ranges

Parameter	Age ≥ 12 to ≤ 15	Age ≥ 16
Systolic Blood Pressure (mmHg)	110 – 131	90 - 120
Diastolic Blood Pressure (mmHg)	64 – 83	60 - 80
Body Temperature (˚C)	35.5 – 37.5	35.5 – 37.5
Respiratory Rate (breaths/min)	12 – 20	12 - 18
Pulse Rate (beats/min)	60 - 100	60 - 100

8. OTHER ANALYSES

Listings on the SAS will be presented for physical examination and comments.

9. INTERIM ANALYSIS/ DATA MONITORING (REVIEW) COMMITTEE

A data safety monitoring board will review the safety and efficacy during the course of the trial, and no formal interim analysis will be performed. Analyses for the data safety monitoring board are described in a separate document.

10. DATA HANDLING CONVENTIONS

10.1 General Data Reporting Conventions

Unless otherwise specified the default summary statistics for quantitative variables will be as follows:

- The number of subjects/surgeries in each category (n).
- Mean.
- Standard deviation (SD).
- Median.
- Minimum.
- Maximum.

The above descriptive statistics will only be presented if there are at least 3 results available in a particular group. All statistics except median will be presented if only 2 results are available in a particular group while only n and mean will be presented if only 1 result is available in a particular group.

If the original data has N decimal places (as derived from the raw data) (i.e., decimal precision [N]) then the summary statistics will contain the following decimal places (with a maximum of 3 decimals):

- Minimum and maximum: N decimals.
- Mean and median: N + 1 decimals.
- Standard deviation: N + 2 decimals.

For qualitative variables the number (n) and percentage (%) of subjects in each category will be the default summary presentation. Unless otherwise specified, percentages will be calculated relative to the total number of subjects in the relevant analysis set with data available as described in the latest version of the Output Templates and this SAP.

All values will be rounded using the SAS® function ROUND. All computed percentages will be presented using 1 decimal place.

The default significance level is to be 5%; confidence intervals are to be 95% and all tests are to be two-sided, unless otherwise specified in the description of the analyses.

10.2 Reference Start Date and Study Days

The reference start date for presentation of study days in data listings will be the date of surgery as obtained from the *Planned Surgery* eCRF.

The date of surgery will be referred to as Day 0. For events occurring on Day 0, a distinction will be made whether the event occurred prior to surgery, intraoperatively or postoperatively. The distinction will be made based on the visit where the result is entered on the eCRF (i.e., preoperative visit, intraoperative visit or postoperative visit).

Study day will be derived as:

$$Study\ Day = (Date\ of\ Event) - (Date\ of\ Surgery).$$

10.3 Definition of Baseline

Unless otherwise specified, baseline is defined as the last non-missing (scheduled or unscheduled) measurement obtained prior to the first IP administration.

For quantitative measurements where change from baseline is presented, change from baseline will be derived as:

$$Change\ from\ Baseline\ at\ Timepoint\ X = (Value\ at\ Timepoint\ X) - (Value\ at\ Baseline)$$

10.4 Repeated or Unscheduled Assessments

In the case of retests, the last available measurement for that visit will be used for by-visit summaries.

Unscheduled results will not be included in summaries.

All results will be presented in listings.

10.5 Handling of Missing, Unused, and Spurious Data

No imputations, other than the below, will be performed for this study.

For surgeries with ≤ 2 missing hemostatic assessments that did not necessitate the use of bypassing agents (FEIBA and NovoSeven) as rescue therapies between the date of the first dose of BAX 802 (inclusive) and the date of the last GHEA assessment on Day 14 (inclusive), the rating of "fair" will be imputed for the missing assessments.

Missing data will be presented as "Not reported" in outputs and no distinction will be made on why the data is missing in the outputs.

11. ANALYSIS SOFTWARE

Statistical analyses will be performed using Version 9.4 of SAS® .

12. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

The Sponsor discontinued the study after 9 out of the 12 planned subjects were enrolled. At the time of study discontinuation, 8 subjects received BAX 802 dosing and 7 of those subjects proceeded to surgery (each subject underwent one surgery). One subject who received BAX 802 dosing was not taken to surgery as they did not reach the prespecified FVIII levels even after booster dosing.

Given this information the following changes were made to the analyses specified in the protocol:

- Due to the possibility of a subject undergoing multiple surgeries, the protocol-specified statistical analysis of efficacy measures was planned to be conducted at the surgery level. However, at the time of study discontinuation, each enrolled subject had undergone only one surgery each. Thus, analyses conducted at the surgery or subject level would be equivalent, with each subject contributing one surgery to the analysis. As a result, FAS was updated to be defined at the subject-

level and the supplementary analysis using the first surgery per subject was removed.

- At the time of study discontinuation, one subject who received BAX 802 dosing was not taken to surgery as they did not reach the prespecified FVIII levels even after booster dosing. The protocol-specified statistical analysis excludes this subject from FAS, the primary efficacy analysis set. Thus, the Dosed in preparation for surgery Analysis Set (DAS) was added to the SAP as a sensitivity analysis. The DAS is defined as all subjects dosed in preparation for surgery. If a subject was dosed in preparation for surgery and did not met the required FVIII levels to proceed with surgery with either the initial dose or supplemental dose, the subject was considered "not successful" for the evaluation of hemostatic efficacy.

13. REFERENCES

Not applicable.

14. Appendices

14.1 Combination of Individual Efficacy Assessment

Table 3 Combination of Individual Efficacy Assessments

GHEA1 Result	GHEA2 Result	GHEA3 Result	GHEA Result
Excellent	Excellent	Excellent	Excellent
Excellent	Excellent	Good	Excellent
Excellent	Good	Good	Excellent
Excellent	Excellent	Fair	Good
Excellent	Good	Fair	Good
Excellent	Fair	Fair	Good
Good	Good	Good	Good
Good	Good	Fair	Good
Good	Fair	Fair	Fair
Fair	Fair	Fair	Fair
Excellent	Excellent	None	None
Excellent	Good	None	None
Excellent	Fair	None	None
Excellent	None	None	None
Good	Good	None	None
Good	Fair	None	None
Good	None	None	None
Fair	Fair	None	None
Fair	None	None	None
None	None	None	None

Above combinations determined by setting "Excellent" to 3, "Good" to 2, "Fair" to 1 and "None" to 0 for GHEA1, GHEA2 and GHEA3. The sum is determined for GHEA.

- If the sum is 7 to 9 with no category scoring less than 2 the GHEA is "Excellent".
- If the sum is 5 to 7 (where the 7 did not fit in the "Excellent" criteria) and no category scored 0 then GHEA is "Good".
- If the sum is 3 to 4 with no category scored 0 then GHEA is "Fair".
- If the sum is 0 to 2 or there is at least one category that scored 0 the GHEA is "None".

As detailed in Section 10.5, surgeries with ≤ 2 missing hemostatic assessments that did not necessitate rescue therapies will have the rating of "fair" imputed for the missing assessments.

Additional details of the ratings are provided in the following tables extracted from the protocol.

Table 4
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 5
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 6
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 7
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