STATISTICAL ANALYSIS PLAN

BAX326 (rFIX)
PHASE 3

BAX326 (recombinant Factor IX): Evaluation of Safety, Immunogenicity, and Hemostatic Efficacy in Previously Treated Patients with Severe (FIX level < 1%) or Moderately Severe (FIX level 1-2%) Hemophilia B – A Continuation Study

PROTOCOL IDENTIFIER: 251001

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1. INTRODUCTION AND OBJECTIVES

This document presents the statistical analysis plan for study 251001 "BAX326 (recombinant Factor IX): Evaluation of Safety, Immunogenicity, and Hemostatic Efficacy in Previously Treated Patients with Severe (FIX level < 1%) or Moderately Severe (FIX level 1-2%) Hemophilia B – A Continuation Study."

1.1 Study Objectives

The objectives of this study are:

- To further evaluate safety of BAX326 in terms of investigational product (IP) related adverse events (AEs) as well as clinically significant changes in routine laboratory parameters (hematology/clinical chemistry) and vital signs.
- To further evaluate the hemostatic efficacy of BAX326 in the prevention and routine prophylaxis of acute bleeding episodes using various dose regimens.
- To further evaluate the hemostatic efficacy of BAX326 in the management of acute bleeding episodes.
- To further evaluate the immunogenicity of BAX326 for up to 100 exposure days (EDs) to BAX326.
- To monitor incremental recovery (IR) of BAX326 over time.
- To evaluate changes in health-related quality of life (HR QoL), Patient Activity Level and health resource use.
- Exploratory: To correlate pre-infusion thrombin generation assay (TGA) parameters with pre-infusion FIX levels and spontaneous breakthrough bleeds in a subset of subjects receiving twice weekly standard or modified prophylaxis including pharmacokinetic (PK) tailored prophylaxis.

2. STUDY DESIGN

This continuation study is a prospective, open-label, multicenter, uncontrolled, phase 3 study in approximately 100 previously treated patients (PTPs) with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) hemophilia B, who have completed either the pivotal Phase 1/3 BAX326 protocol 250901 or the pediatric protocol 251101 (Cohort 1) as well as in approximately 25 BAX326 naïve subjects (Cohort 2).

Any subject requiring elective or emergency surgery may be temporarily transitioned to the BAX326 Surgery Study (# 251002) for peri- and postoperative hemostatic management. Exemptions may be granted for minor interventions. As soon as the subject is discharged from the (surgical) study site, he will be switched back to this continuation study until completion. For subjects switching back to this study from the surgery study, the respective visit window may be extended from ± 1 week to ± 2 weeks. Outside this window, an additional end-of-study visit for the surgery study must be arranged. Once the surgery study is completed, all surgeries for subjects must be approved by the sponsor. If not approved, the subject will be withdrawn from further study participation.

This continuation study will consist of two cohorts both with the option for subjects to be treated on standard, modified or PK-tailored prophylaxis. Subjects in cohort 1 can also be on an on-demand treatment regimen.

2.1 Cohort 1: Subjects Transitioning from BAX326 Pivotal or BAX326 Pediatric Study

All subjects who completed Baxter Pivotal Study 250901 or Pediatric Study 251101 have an option to enroll in the continuation study (Cohort 1). The treatment regimen with BAX326 will be at the discretion of the investigator and will consist of one of the following treatment options:

- Standard prophylaxis with twice weekly prophylactic infusions of 50 IU/kg (range of 40-60 IU/kg, which may be increased to 75 IU/kg, in subjects ≥ 12 years of age; range of 40-80 IU/kg in pediatric subjects < 12 years), or
- modified prophylaxis determined by the investigator. The dose can be increased up to 100 IU/kg, if applicable; or
- PK-tailored prophylaxis based on subject's individual pharmacokinetics (PK). The maximum dose is 120 IU/kg; or
- on-demand treatment.

The screening visit for the continuation study will be performed on the same day as the end of study/termination visit of the pivotal or pediatric study in order to ensure continuity of BAX326 therapy. Subjects can be given the Informed Consent Form prior to the termination visit of Pivotal Study 250901 or Pediatric Study 251101 to ensure ample time for reviewing and considering the participation in the continuation study 251001. Subjects will be supplied with IP for a maximum of 5 weeks at the screening visit. The subject will then return to the study site no later than 4 ± 1 weeks to review the results of the screening visit (including results from termination visits for Study 250901 or 251101), and confirm their eligibility for continued participation.

2.2 Cohort 2: Newly Recruited Subjects

At least 25 subjects who have not previously been exposed to BAX326 will be enrolled (Cohort 2). Once eligibility criteria are confirmed, subjects will receive prophylactic treatment over a period of up to approximately 100 EDs to BAX326, or until BAX326 is approved in the subject's country, whichever occurs last, but no later than December 31, 2016. A limited number of patients may not have reached 100 EDs by that date and they will continue until they have reached approximately 100 EDs. The treatment regimen with BAX326 will be at the discretion of the investigator and will consist of one of the following treatment options:

- Standard prophylaxis with twice weekly prophylactic infusions of 50 IU/kg (range of 40-60 IU/kg, which may be increased to 75 IU/kg, in subjects ≥ 12 years of age; range of 40-80 IU/kg in pediatric subjects < 12 years), or
- modified prophylaxis determined by the investigator. The dose can be increased up to 100 IU/kg, if applicable; or
- PK-tailored prophylaxis. The maximum dose is 120 IU/kg.

2.3 Study Population

Previously treated patients (PTPs) with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) hemophilia B, who completed Pivotal Study 250901 or Pediatric Study 251101, and were between 12 and 65 years of age at the time of screening for Study 250901 or < 12 years old at the time of screening for Study 251101, will be recruited in this study (Cohort 1 patients).

In addition, at least 25 BAX326 naïve subjects with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) hemophilia B will be newly enrolled to ensure the evaluation of long-term safey and efficacy in approximately 100 PTPs (Cohort 2 patients).

2.4 Inclusion Criteria

2.4.1 Subjects Transitioning From Baxter Pivotal Study 250901 or Pediatric Study 251101 (Cohort 1)

Subjects who have completed Baxter Pivotal Study 250901 or Pediatric Study 251101 and meet **ALL** of the following criteria are eligible for this study:

1. Subject and/or legal representative has/have voluntarily provided signed informed consent.
2. Subject has completed Baxter Pivotal Study 250901 or Pediatric Study 251101.
3. Subject has not developed an inhibitory FIX antibody during Baxter Pivotal Study 250901 or Pediatric Study 251101.
4. Subject is human immunodeficiency (HIV) negative or is HIV+ with a viral load < 200 particles/μL ~ < 400,000 copies/mL.
5. Subject is immunocompetent as evidenced by a CD4 count ≥ 200 cells/mm^3.
6. If female of childbearing potential, subject presents with a negative pregnancy test and agrees to continue employing adequate birth control measures for the duration of the study.
7. Subject is willing and able to comply with the requirements of the protocol.

2.4.2 Newly Recruited Subjects (Cohort 2)

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

1. Subject and/or legal representative has/have provided signed informed consent.
2. Subject is 2 to 70 years old at the time of screening.
3. Subject is naïve to BAX326.
4. Subject has severe (FIX level < 1%) or moderately severe (FIX level 1-2%) hemophilia B (based on the one stage activated partial thromboplastin time (aPTT) assay), as tested at screening at the central laboratory.
5. Subject aged ≥ 6 years has been previously treated with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 150 EDs.
6. Subject aged < 6 years has been previously treated with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 50 EDs.
7. Subject has no evidence of a history of FIX inhibitors.
8. Subject is immunocompetent as evidenced by a CD4 count ≥ 200 cells/mm^3 at screening.

9. Subject is HIV negative or is HIV+ with a viral load < 200 particles/μL ~ < 400,000 copies/mL.
10. If female of childbearing potential, subject presents with a negative pregnancy test and agrees to employ adequate birth control measures for the duration of the study.
11. Subject is willing and able to comply with the requirements of the protocol.

2.5 Exclusion Criteria

2.5.1 Subjects Transitioning from Pivotal Study 250901 or Pediatric Study 251101 (Cohort 1)

Subjects who have completed Baxter Pivotal Study 250901 or Pediatric Study 251101 and meet **ANY** of the following criteria are not eligible for this study:

1. Subject received factor IX product(s) other than BAX326 upon completion of Baxter Pivotal Study 250901 or Pediatric Study 251101.
2. Subject has been diagnosed with an acquired hemostatic defect other than hemophilia B.
3. For subjects transferring from Pivotal Study 250901: The subject's weight is < 35 kg or > 120 kg.
4. Subject's platelet count is < 100,000/mL.
5. Subject has an abnormal renal function (serum creatinine > 1.5 times the upper limit of normal).
6. Subject has active hepatic disease with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥ 5 times the upper limit of normal.
7. Subject is scheduled to receive during the course of the study, an immunomodulating drug (e.g. corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day, or α-interferon) other than anti-retroviral chemotherapy.
8. Subject has a clinically significant medical, psychiatric, or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject's safety or compliance.
9. Subject is planned to take part in any other clinical study, with the exception of BAX326 Surgery Study as described in this protocol, during the course of the Continuation Study.
10. Subject is a member of the team conducting this study or is in a dependent relationship with one of the study team members. Dependent relationships include

close relatives (ie, children, partner/spouse, siblings, parents) as well as employees of the investigator or site personnel conducting the study.

2.5.2 Newly Recruited Subjects (Cohort 2)

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

1. Subject has a history of FIX inhibitors with a titer ≥ 0.6 Bethesda Units (BU) (as determined by the Nijmegen modification of the Bethesda assay or the assay employed in the respective local laboratory) at any time prior to screening.
2. Subject has a detectable FIX inhibitor at screening, with a titer ≥ 0.6 BU as determined by the Nijmegen modification of the Bethesda assay in the central laboratory.
3. Subjects ≥ 12 years of age: Subject's weight is < 35 kg or > 120 kg.
4. Subject has a history of allergic reaction, eg, anaphylaxis, following exposure to FIX concentrate(s).
5. Subject has a known hypersensitivity to hamster proteins or rFurin.
6. Subject has evidence of an ongoing or recent thrombotic disease, fibrinolysis or disseminated intravascular coagulation (DIC).
7. Subject has an abnormal renal function (serum creatinine > 1.5 times the upper limit of normal).
8. Subject has severe chronic liver disease as evidenced by, but not limited to, any of the following: International Normalized Ratio (INR) > 1.4 hypoalbuminemia, portal vein hypertension including presence of otherwise unexplained splenomegaly and history of esophageal varices.
9. Subject has active hepatic disease with ALT or AST levels > 5 times the upper limit of normal.
10. Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia B.
11. Subject's platelet count is < 100,000/mL.
12. Subject has a clinically significant medical, psychiatric, or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject's safety or compliance.
13. Subject is currently receiving, or is scheduled to receive during the course of the study, an immunomodulating drug (eg, corticosteroid agents at a dose equivalent

to hydrocortisone greater than 10 mg/day, or α-interferon) other than anti-retroviral chemotherapy.

14. Subject has participated in another investigational study within 30 days of enrollment.
15. Subject is a member of the team conducting this study or is in a dependent relationship with one of the study team members. Dependent relationships include close relatives (ie, children, partner/spouse, siblings, parents) as well as employees of the investigator or site personnel conducting the study.

2.6 Sample Size and Power Calculations

The sample size is not based on statistical consideration and is determined by the number of subjects of the BAX326 pivotal protocol 250901 and the pediatric protocol 251101, who are willing to participate in this study and meet the eligibility criteria as well as regulatory requirements.

2.7 Randomization and Blinding

This section is not applicable.

2.8 Study Stopping Rules

This study will be halted, pending further review by the sponsor, or stopped under the following circumstances:

- If two or more subjects develop a high titer inhibitory antibody > 5 BU confirmed by the central laboratory, or if two or more subjects develop anaphylaxis following exposure to BAX326 in studies BAX326 Pivotal 250901, BAX326 Pediatric 251101, and BAX326 Continuation 251001, the transition to BAX326 Continuation will be halted. Within 2 weeks of receipt of the second report, Baxalta may decide to halt the study.
- The study may be stopped following any of the planned interim safety reviews or at any time by the sponsor in case of unacceptable risks to subjects, in particular in case of inhibitor development, thrombotic events, or anaphylaxis.

2.9 Data Monitoring Committee

The safety of BAX326 in this study will be monitored by an independent Data Monitoring Committee (DMC) as scheduled until the end of 2015. The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. For this study, the DMC will be composed of recognized experts in the field of hemophilia clinical care and research who are not actively recruiting subjects, and an independent statistician.

The sponsor will formally convene this panel for review of the study data at least once per year until completion of the study. From the beginning of 2016 onwards, the DMC chair will no longer review all SAEs for all subjects as sufficient positive safety data from pre- and post-marketing BAX326 exposures are already available.

The study may be stopped at any time by the sponsor in case of unacceptable risks to subjects, in particular in case of inhibitor development, thrombotic events, or anaphylaxis.

3. STUDY OUTCOME MEASURES

3.1 Primary Outcome Measure

The primary outcome measure is AEs possibly or probably related to IP.

3.2 Secondary Outcome Measures

3.2.1 Hemostatic Efficacy

- Treatment of bleeding episodes:
  - Number of infusions per bleeding episode
  - Overall hemostatic efficacy rating at resolution of bleed
- Prophylaxis:
  - Annualized bleeding rate (ABR)
- Consumption of BAX326:
  - Number of infusions and weight-adjusted consumption per month and per year
  - Weight-adjusted consumption per event (for prophylaxis and on-demand)

3.2.2 Safety and Immungenicity

- Development of inhibitory and total binding antibodies to FIX
- Development of antibodies to CHO proteins and rFurin
- Occurrence of severe allergic reactions, e.g. anaphylaxis
- Occurrence of thrombotic events
- Clinically significant changes in routine laboratory parameters (hematology and clinical chemistry), and vital signs

3.2.3 Pharmacokinetics

- IR (incremental recovery) over time

If subject receives a PK-tailored dose regimen and did not participate in the PK portion of the BAX326 pivotal or BAX326 surgery study, then the following parameters will be calculated:

- AUC0-∞ (area under the plasma concentration time curve from time 0 to infinity), T1/2 (elimination phase half-life), MRT (mean residence time), CL (clearance), Vss (volume of distribution at steady state) and IR (incremental recovery)

3.2.4 Health-Related Quality of Life and Pharmacoeconomics

The assessment of HR QoL based on 4 questionnaires will be performed every 6 months ± 1 week. Newly recruited subjects will have their first HrQoL assessment including Patient Activity Level performed prior to or following the first infusion with BAX326, thereafter every 6 months.

The capture of health resource use will be performed by a named member of study site staff every 3 months ± 1 week. Newly recruited subjects will have their first health resource use capture prior to or following the first infusion with BAX326, thereafter at every 3 months ± 1 week.

Data on HR QoL and Health Resource Use will be collected using the instruments shown in the following table, with some instruments having an age specific version.

Table 1: Age specific instruments used for HR QoL and Health Resource Use

	Age Group (Age at the time of screening for Pediatric Study 251101 for Cohort 1 subjects or at the time of screening for Study 251001 for Cohort 2 subjects)			
Instrument	2 to 7 years	8 to 11 years	12 to 16 years	17 years and older
Leisure Time Exercise Questionnaire (Patient Activity Level)	Yes	Yes	Yes	Yes
Health Resource Use	Yes	Yes	Yes	Yes
Generic: PedsQL™	Yes: Parent-proxy versions (age groups: 2-4years and 5-7 years)	Yes: Child version	Yes	NA
Disease-specific: Haemo-QoL	NA	Yes: Short version	Yes: Short version	Yes
General pain assessment through a visual analog scale (VAS)	NA	NA	Yes	Yes
Health utility: EQ-5D	NA	NA	Yes	Yes
Generic: SF-36	NA	NA	NA	Yes

3.2.5 Exploratory Outcomes Measures

- If applicable, TGA parameters over 72 hours during PK (lag time, time to peak thrombin generation, peak thrombin generation, endogenous thrombin potential [ETP])

- TGA parameters pre- and post-infusion concurrent with IR determination for FIX activity in a subset of subjects receiving twice-weekly standard or modified prophylaxis including PK-tailored prophylaxis with BAX326 as well as at some selected time points during prophylactic treatment

4. ANALYSIS SETS

4.1 Full Analysis Set

The Full Analysis Set (FAS) will be comprised of all subjects who are exposed to any amount of IP. For subjects who discontinue before reaching 100 EDs, data will be included up through the day of discontinuation. The FAS will be used for all analyses unless otherwise stated.

4.2 Per Protocol Analysis Set

The Per Protocol Analysis Dataset (PPAS) is defined as a subset of the Full Analysis Set.

1. Transitioning Subjects:

Subjects who did not meet study inclusion criteria

- The subject has severe (FIX level <1%) or moderately severe (FIX level ≤2%) hemophilia B (based on the one stage activated partial thromboplastin time (aPTT) assay), as tested at screening at the central laboratory
- The subject has not developed an inhibitory FIX antibody during Baxter clinical study 250901
- The subject has not developed an inhibitory FIX antibody during Baxter Pivotal Study 250901 or Pediatric Study 251101

or met the exclusion criteria

- The subject has been diagnosed with an acquired hemostatic defect other than hemophilia B.
- The subject´s platelet count is <100,000/mL.

will be excluded from the PPAS.

2. Newly Recruited Subjects:

Subjects who did not meet study inclusion criteria

- The subject has severe (FIX level <1%) or moderately severe (FIX level 1-2%) hemophilia B (based on the one stage activated partial thromboplastin time (aPTT) assay), as tested at screening at the central laboratory
- The subject has no evidence of a history of FIX inhibitors

or met the exclusion criteria

- The subject has a history of FIX inhibitors with a titer ≥0.6 Bethesda Units (BU) (as determined by the Nijmegen modification of the Bethesda assay or the assay employed in the respective local laboratory) at any time prior to screening
- The subject has a detectable FIX inhibitor at screening with a titer ≥0.6 BU as determined by the Nijmegen modification of the Bethesda assay in the central laboratory
- The subject has severe chronic liver disease as evidenced by, but not limited to, any of the following: International Normalized Ratio (INR) > 1.4, hypoalbuminemia, portal vein hypertension including presence of otherwise unexplained splenomegaly and history of esophageal varices.
- The subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia B.
- The subject´s platelet count is <100,000/mL

will be excluded from the PPAS.

4.3 Pharmacokinetic Full Analysis Set

The Pharmacokinetic Full Analysis Set (PKFAS) will be comprised of all subjects in the FAS who underwent an abbreviated PK study.

5. STATISTICAL CONSIDERATIONS

Safety, efficacy, PK, HRQoL and immunogenicity data from the additional BAX326 naïve subjects (Cohort 2) will be analyzed together with the data from the previously treated subjects (Cohort 1).

The pediatric (< 12 years) and the adolescent/adult (≥ 12 years) data (i.e. age group 1) will be summarized separately and overall for all outcome measures except for analyses mentioned in section 10, section 11 and pharmacokinetic analyses (it turned out that only adults underwent an abbreviated PK study). Further analyses will occur between the age groups <6 years, ≥6 to <12 years, ≥12 to <18 and ≥18 (i.e. age group 2) for all outcome measures except for analyses mentioned in section 10, section 11.1 and pharmacokinetic analyses.

In case it is specified that analyses for a specific outcome measure will also be presented by treatment regimen, the summary statistics should be presented by individual treatment regimen (standard prophylaxis, modified prophylaxis, PK-tailored prophylaxis and on-demand treatment) as well as for overall prophylaxis (combined standard, modified and PK-tailored prophylaxis).

If a subject changes regimen during the course of the study, then the data from that subject will be analyzed under the initial allocated regimen until a change of regimen is recorded. Data recorded after this stage will be analyzed under the updated regimen.

In general, all efficacy, safety, PK, HRQoL and immunogenicity variables will be summarized using descriptive statistics. Continuous variables will be summarized by sample size [n], mean, standard deviation [SD], median, minimum, maximum, Q1 and Q3. Categorical variables will be summarized in frequency tables (n, frequencies, and percentages). Additional statistics which will be provided for specific endpoints will be described in the corresponding section.

5.1 Interim Analyses

An interim safety review may be performed after a minimum of 50 subjects have accumulated a total of at least 100 EDs to BAX326 for evaluation of long-term hemostatic efficacy, safety, immunogenicity and HrQoL.

5.2 Handling of Missing, Unused, and Spurious Data

Statistical techniques will not be used to identify and exclude any observations as outliers from the analyses. If data are considered spurious (e.g. for lack of biological plausibility), it will be documented along with the reason for exclusion and the analyses from which the data were excluded.

1. For subjects with multiple screening visits resulting in multiple values, the most recent screening visit will be used for analysis.

2. Subjects who withdraw prior to the last planned observation in the study period will be included in the analyses up to the time of withdrawal.

3. Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics, but will be included in subject listings.

4. If a subject's weight is missing from any infusion record, the subject's last recorded weight will be used to calculate the weight-adjusted dose.

Outcome specific handling of missing data are described in the relevant section. Unless otherwise specified, no action will be made to handle missing data (observed case).

5.3 Definition of Baseline

The most recent value prior to first infusion of IP will be taken as baseline.

5.4 Definition of Visit Windows

All available values will be used in the statistical analysis independent of whether they are within or outside the pre-defined visit windows. No specific visit windows will be defined for the statistical analysis.

5.5 Changes from the Planned Statistical Analysis in Protocol

The following changes from the planned statistical analysis in the protocol were made:

- In some instances, techniques will be used to adjust for missing data.
- In addition to the Full Analysis Set, a Per Protocol Analysis Set and a Pharmacokinetic Full Analysis Set were added.
- Pharmacokinetic parameters will be calculated using non-compartmental analysis (NCA), rather than a model combining data from this and previous studies, due to the lack of a suitable model.
- In order to determine the incremental recovery (IR) over time and see if antibodies have affected the recovery following long-term exposure, it is important to compare the end of study IR with the baseline IR. Therefore the IR will be summarized for baseline and end of study only rather than for all available time points.

6. STUDY SUBJECTS

6.1 Disposition of Subjects

The number (%) of subjects who were enrolled and treated will be summarized overall, by cohort and by treatment regimen. The number (%) of subjects who completed the study, or discontinued for any reason will also be summarized overall, by cohort and by treatment regimen. The details of the discontinued subjects will be presented in a listing with the reason for discontinuation. Subject disposition will also be presented by study site.

The number of subjects in each specific data set will be summarized by treatment regimen as well as for all treatment regimens together. Details of subjects excluded from any data set will be listed.

A disposition flowchart will be included.

A by-subject listing of lot numbers used will be provided.

6.2 Demographic and Baseline Characteristics

Demographic data will be summarized descriptively and listed by treatment regimen as well as for all treatment regimens together:

- Age at Screening
- Age at Screening of Parent Protocol (applicable only for transitioning subjects)
- Gender
- Ethnicity (for US only)
- Race
- Height [cm] at Screening
- Weight [kg] at Screening
- Body mass index (BMI) [kg/m^2] at Screening.

Demographic variables will be summarized for the FAS, the PPAS and the PKFAS.

6.3 Medical History

Medical history will be listed for subjects in the FAS.

6.4 Prior Therapies and Medication

Prior therapies and medication will be listed for subjects in the FAS.

6.5 Concomitant Medications

Concomitant medications, non-drug therapies and hemostatic products other than BAX326 will be listed for subjects in the FAS.

6.6 Measurements of Treatment Compliance

Treatment compliance for subjects on prophylaxis will be summarized on the FAS and a subject-level listing will also be provided.

The compliance measures regarding frequencies are:

- Standard prophylaxis: number of prophylaxis infusions within 2.5-4.5 days of previous infusion / total number of standard prophylaxis infusions
- PK-tailored prophylaxis: number of PK-tailored prophylaxis infusions within 6-8 days of previous infusion / total number of PK-tailored prophylaxis infusions

The compliance measures regarding dose limits are:

- Standard prophylaxis:
    - Subjects ≥ 12 years: number of prophylaxis infusions within 40-75 IU/kg / total number of standard prophylaxis infusions
    - Subjects < 12 years: number of prophylaxis infusions within 40-80 IU/kg / total number of standard prophylaxis infusions
- Modified prophylaxis: number of modified prophylaxis infusions ≤ 100 IU/kg / total number of modified prophylaxis infusions
- PK-tailored prophylaxis: number of PK-tailored prophylaxis infusions ≤ 120 IU/kg / total number of PK-tailored prophylaxis infusions

The compliance measures regarding prescribed doses are:

- Standard prophylaxis: number of prophylaxis infusions within 10% of the prescribed dose / total number of standard prophylaxis infusions
- Modified prophylaxis: number of modified prophylaxis infusions within 10% of the prescribed dose / total number of modified prophylaxis infusions
- PK-tailored prophylaxis: number of PK-tailored prophylaxis infusions within 10% of the prescribed dose / total number of PK-tailored prophylaxis infusions

The compliance measures regarding dose limits and prescribed doses are:

- Standard prophylaxis:
  - Subjects ≥ 12 years: number of prophylaxis infusions within 40-75 IU/kg and within 10% of the prescribed dose / total number of standard prophylaxis infusions
  - Subjects < 12 years: number of prophylaxis infusions within 40-80 IU/kg and within 10% of the prescribed dose / total number of standard prophylaxis infusions
- Modified prophylaxis: number of modified prophylaxis infusions ≤ 100 IU/kg and within 10% of the prescribed dose / total number of modified prophylaxis infusions
- PK-tailored prophylaxis: number of PK-tailored prophylaxis infusions ≤ 120 IU/kg and within 10% of the prescribed dose / total number of PK-tailored prophylaxis infusions

Note that the regimen, dose and/or frequency of dosing may change during the prophylaxis observation period.

6.7 Protocol Deviations

Protocol deviations will be summarized by classification [major/minor], study site and coded deviation term.

7. EFFICACY EVALUATION

The analysis of efficacy endpoints will be performed on the FAS as well as on the PPAS with the analysis on FAS considered the primary analysis.

7.1 Analysis of Primary Efficacy Outcome Measure

There is no primary efficacy outcome measure in this study.

7.2 Analysis of Secondary Efficacy Outcome Measure

7.2.1 Treatment of Bleeding Episodes

Summary statistics will be provided for the overall hemostatic efficacy rating at resolution of bleed as well as for the number of infusions per bleeding episode. These tables will be also presented by bleeding site (joint/non-joint), cause (spontaneous/injury) and severity (minor, moderate, major, and life/limb-threatening). These subgroup analyses will be performed on the FAS only.

As a sensitivity analysis to the assumption of independency between bleeds within the same subject, these summary tables will be also created with the assessment of the first bleed within a specific treatment regimen for each subject. This sensitivity analysis will be performed on the FAS only (and not by bleeding site, cause and severity).

Bleeding episodes, for which any hemostatic product other than BAX326 had to be used, will not be considered.

These tables will be created by treatment regimen as well as for all treatment regimens together.

7.2.2 Prophylaxis: Annualized Bleed Rate

The ABR will be calculated as follows:

$$\frac{\text{Number of bleeding episodes}}{\text{Observed treatment period in days}} * 365.25.$$

The ABR will be listed and summarized only for subjects who have adequate treatment time for bleeding rate assessment. For subjects on prophylaxis, a subject is considered to have an adequate treatment time for bleeding rate assessment if the observation period with BAX326 in this study within the respective treatment regimen was a minimum of 3 months (treatment period for surgery and bleeding period are not counted).

The observation period for prophylactic treatment is considered as the time between the first and the last prophylactic infusions. For transitioning subjects, infusions prior to eligibility assessment will count in case the treatment regimen is the same as the regimen the subject receives after eligibility is confirmed. The treatment period for surgery as well as the bleeding period will be excluded from the calculation of observation period in the calculation.

Additionally, the ABR will also be calculated for subjects with on-demand treatment. The observation period for on-demand treatment is considered as the time between the date of eligibility (or the date of switching to on-demand for subjects who were on prophylaxis before) and the end of observation period.

These tables will be created by treatment regimen.

ABR will be also presented by bleeding site (joint/non-joint), cause (spontaneous/injury), severity (minor, moderate, major, and life/limb-threatening), presence of target joints and FIX activity levels at screening. These subgroup analyses will be performed on the FAS only.

7.2.3 Consumption of BAX326

Summary statistics will be provided for the product consumption of BAX326 by treatment regimen:

- Number of infusions per month and per year
- Weight-adjusted consumption per month and per year
- Weight-adjusted consumption per bleeding event

8. SAFETY EVALUATION

The analysis of safety endpoints will be performed on the FAS.

Regarding missing data in AE records:

- Handling of unknown causality assessment:
    - If a subject experiences an AE with a missing causality assessment, the relationship of the AE will be counted as "related".
- Handling of unknown severity grades:
    - If a subject experiences more than one AE categorized under the same preferred term, one of them is categorized as "severe" and one of them is categorized as "unknown", the severity of this AE should be counted as "severe".
    - If a subject experiences more than one AE categorized under the same preferred term, one of them is categorized as "mild" or "moderate" and one of them is categorized as "unknown", the severity of this AE should be counted as "unknown". A column "UNK" should be inserted for those AEs at the end of the table (before the "Total" column if applicable).

8.1 Analysis of Primary Safety Outcome Measure

The number of possibly or probably related adverse events that occurred during or after first BAX326 infusion will be summarized. In addition, the number of subjects with possibly or probably related adverse events that occurred during or after first BAX326 infusion will be also summarized.

8.1.1 Adverse Events

AEs that occurred during or after first IP infusion will be presented in summary tables. Summary tables shall indicate the number of subjects who experienced adverse events. Separate tables will be carried out for temporally associated adverse events; and for temporally associated or causally related adverse events.

In addition, tables will be prepared to list each AE, the number of subjects who experienced an AE at least once, and the rate of subjects with AE(s). AEs will be grouped by system organ class. Each event will then be divided into defined severity grades (mild, moderate, severe). The tables will also divide the AEs into those considered related (a "possibly related" or a "probably related" AE will be considered as a "related AE") to the treatment and those considered unrelated (an "unlikely related" or a "not related" AE will

be considered as an "unrelated" AE). These tables will also be carried out for temporally associated adverse events; and for temporally associated or causally related adverse events.

All AEs; temporally associated AEs; causally related AEs; and temporally associated or causally related AEs will also be summarized by system organ class, preferred term, including the number of AEs, the number (%) of unique subjects, the frequency category (very common: ≥10%, common: ≥1% to <10%, uncommon: ≥0.1% to <1%, rare: ≥0.01% to <0.1%, very rare: <0.01%) and the number of IP-infusions associated with an AE.

Temporally associated AEs are defined as AEs that begin during infusion or within 24 hours (or 1 day where time of onset is not available) after completion of infusion, irrespective of being related or not related to treatment.

AEs and SAEs for each subject, including the same event on several occasions, will be listed separately, giving both MedDRA preferred term and the original term used by the investigator, system organ class, severity grade, seriousness, relation to the treatment, onset date, and stop date.

AEs that occurred before first IP infusion will be listed separately.

8.2 Analysis of Secondary Safety Outcome Measures

A table will present the number (%) of subjects for the following safety endpoints: occurrence of inhibitory and (treatment emergent) total binding antibodies to FIX, occurrence of (treatment emergent) antibodies to CHO proteins and rFurin, occurrence of severe allergic reactions (e.g. anaphylaxis), and occurrence of thrombotic events.

As mentioned in section 12.7.1 of the protocol, indeterminate results of total binding antibodies to FIX, antibodies to CHO proteins or rFurin will be set to negative. Occurrence of treatment emergent total binding antibodies to FIX, antibodies to CHO proteins and rFurin is defined by more than 2-dilution increase as compared to levels at screening visit (e.g. negative to 1:80).

8.2.1 Hematology and Clinical Chemistry Laboratory Evaluations

For each hematology and clinical chemistry laboratory assay, shift tables will display two way frequencies for the number of abnormal/normal values from the screening, compared to the assessment at end of study. For abnormal values, frequencies will be split up by clinical significance. All abnormal hematology and clinical chemistry result will be listed, giving units of measurement and clinical relevance of result provided by investigators.

8.2.2 Vital Signs

A summary table of changes in vital signs (pulse rate, systolic/diastolic blood pressure, respiratory rate, body temperature) from pre-infusion to end of study will be provided.

The percent change in vital signs will be calculated as:

((vital_sign2-vital_sign1)/vital_sign1)*100;

where vital_sign1 denotes the vital sign value at the pre-infusion time-point and vital_sign2 denotes the end of study vital sign value.

8.3 Extent of Exposure

A summary table of BAX326 exposure days (EDs) will be created by treatment regimen as well as for all treatment regimens together. Exposure days (after study entry of the Continuation study) during the surgery study (251002) should be taken into account.

8.4 Viral Serology

Each viral marker test will be summarized using a shift table between the screening and the termination visits. Any changes from the assessment at the screening visit will also be listed.

9. EVALUATION OF PHARMACOKINETICS

All PK analyses will use the actual sampling times, not nominal times specified in the protocol, wherever possible. Actual sampling times will be defined as time from the start of infusion to the blood sample collection time. A deviation from the protocol-specified drawing time window will not be a reason to exclude an observation. Samples with unknown actual and planned collection date/time and/or where the concentration could not be determined, or where results were biological implausible will be eliminated before the calculations.

The pediatric (< 12 years) and the adolescent/adult (≥ 12 years) data will be summarized separately.

Regarding missing values / values below the lower limit of quantification (LLOQ):

- FIX activity level:
  - If pre-infusion / post-infusion value is missing then no imputation will be done.
  - If pre-infusion value reported as < 1% (i.e. LLOQ):
    - For calculation of IR over time, use 0.5%.
    - For descriptive statistics, use 0.5%.
    - For calculation of PK parameters, use 0%.
  - If post-infusion value reported as < 1% (i.e. LLOQ):
    - For descriptive statistics, use 0.5%.
    - For calculation of PK parameters, remove value from the calculation of PK parameters.
- Time:
  - Missing start time of infusion:
    - If stop time and actual collection time are available, then stop time of infusion will be taken for further calculation (i.e. time difference between actual end date/time of infusion and date/time blood sample drawn).
    - If stop time and/or actual collection time is not available and planned collection date/time is available, then use planned collection date/time.
    - Otherwise, this PK sample will be taken out from the PK analysis.
  - Missing actual collection date/time:
    - If planned collection date/time is available, then use planned collection date/time.
    - Otherwise, this PK sample will be taken out from the PK analysis.

9.1 IR Over Time

Analysis of IR over time will be carried out on the FAS.

IR_{30min} in IU/dL/IU/kg will be calculated as:

$$\text{IR30min} = \frac{C_{30min}[IU/dL] - C_{pre-infusion}[IU/dL]}{dose\ per\ kg\ body\ weight\ [IU/kg]}$$

where C_{30min} and $C_{pre\text{-}infusion}$ relate to the unadjusted concentration values.

IR_{30min} of FIX will be summarized for baseline and end of study using descriptive statistics. Also the change from baseline to end of study will be described using summary statistics.

These tables will be created for the on-demand treatment only (i.e. subjects who received on-demand treatment exclusively over the whole study period), for the overall prophylaxis (combined standard, modified and PK-tailored prophylaxis) only, for subjects who received on-demand treatment and any prophylaxis treatment (i.e. subjects who switched during the study) as well as for all treatment regimens together.

In addition, IR_{30min} of FIX will be provided in a by-subject listing.

The maximum allowable dose is 120 IU/kg – all cases with a dosage higher than 120 IU/kg will be excluded from the IR tables and will be only displayed in a listing.

9.2 PK Parameters from Abbreviated PK Study

Analysis of PK parameters will be performed on the PKFAS.

To ensure that FIX levels at pre-infusion are not affecting the estimation of PK parameters, post-infusion concentration data will be adjusted proportionally as follows:

$$FIX_{Adjusted,t} = \left(1 - \frac{FIX_{Measures,pre-infusion}}{C_{max}}\right) * FIX_{Measured,t}$$

Area under the plasma concentration/time curve from time 0 to 72 hours ($AUC_{0\text{-}72h}$) in IU·hr/dL will be computed using the linear trapezoidal method. The concentration at 72 hours will be interpolated from the two nearest sampling time points or extrapolated using the last quantifiable concentration and the terminal rate constant λz. λz will be estimated from the

slope of natural log-linear fitting to latter quantifiable concentrations, with largest adjusted R^2.

Area under the plasma concentration/time curve from time 0 to infinity ($AUC_{0-\infty}$) in IU·hr/dL will be defined as AUC_{0-t} + Ct/ λz, where t is the time of last quantifiable concentration, Ct is the last quantifiable concentration.

Elimination phase half-life ($T_{1/2}$) in hours will be calculated as

$$T_{1/2} = log_e(2)/\lambda_z$$

where the elimination rate constant (λ_z) will be obtained by log_e-linear fitting using least squares deviations to at least the last 3 quantifiable concentrations above pre-infusion level.

The **Mean Residence Time** (MRT) in hours will be calculated as total area under the moment curve divided by the total area under the curve:

$$MRT = \frac{AUMC_{0-\infty}[h^2 * IU/dL]}{AUC_{0-\infty}[h * IU/dL]} - \text{TI}/2$$

where $AUMC_{0-\infty}$ will be determined in a similar manner as $AUC_{0-\infty}$ and TI represents infusion duration [hr].

Systemic clearance (Cl) in dL/kg/hours will be calculated as the dose in IU/kg divided by the total AUC:

$$CL = \frac{Dose[IU/kg]}{AUC_{0-\infty}[h * IU/dL]}$$

Apparent **steady state volume of distribution** (Vss) in dL/kg will be calculated as:

$$Vss = \frac{Dose[IU/kg] \times AUMC_{0-\infty}[h^2 * IU/dL]}{AUC^2_{0-\infty}[h^2 * IU^2/dL^2]} = \text{CL} * \text{MRT}$$

The **maximum concentration**, C_{max}, will be calculated as the maximum concentration post-infusion.

The **time to reach the maximum concentration**, T_{max}, in hours was defined as the time to reach C_{max}.

$AUC_{0-\infty}$, $AUC_{0-\infty}$/Dose, AUC_{0-72h}, AUC_{0-72h}/Dose, $T_{1/2}$ (elimination phase half-life), MRT (mean residence time), CL (clearance), Vss (volume of distribution at a steady state), C_{max} (maximum concentration), T_{max} (time to reach the maximum concentration) and IR (incremental recovery), will be summarized using descriptive statistics. Additionally, IR of FIX will be displayed graphically over time for each subject.

In addition, by-subject plots of FIX level against time will be presented on the linear and semi-logarithmic scales.

PK parameters will be derived using non-compartmental methods in WinNonlin® Version 6.2, or higher. Detailed specifications around the PK calculation is described in a separate document that was generated for the dosing recommendations.

10. EVALUATION OF QUALITY OF LIFE

The analysis of quality of life outcomes and health resource use will be performed on the FAS.

10.1 Health Related Quality of Life

Transitioning subjects (cohort 1) continue to use the HRQoL questionnaires used in the parent study, even if they transition to an older age group in this study. Newly recruited subjects (cohort 2) continue using the same HRQoL questionnaires used at their screening visit for this study, even if they transition to an older age group later in the study.

HR QoL assessments and the change from baseline to end of study will be summarized.

These tables will be created for the on-demand treatment only (i.e. subjects who received on-demand treatment exclusively over the whole study period), for the overall prophylaxis (combined standard, modified and PK-tailored prophylaxis) only as well as for subjects who received on-demand treatment and any prophylaxis treatment (i.e. subjects who switched during the study).

10.2 Health Resource Use

The analysis of health resource use will be descriptive in nature. The total number of hospitalizations, emergency room visits, unscheduled physician office visits and days missed from work/school will be reported. Additional analyses include mean hospitalizations per subject, mean length of stay and mean number of days missed from work/school.

These tables will be created per subject year for the on-demand treatment only (i.e. subjects who received on-demand treatment exclusively over the whole study period), for the overall prophylaxis (combined standard, modified and PK-tailored prophylaxis) only as well as for subjects who received on-demand treatment and any prophylaxis treatment (i.e. subjects who switched during the study).

11. EVALUATION OF EXPLORATORY OUTCOME MEASURES

11.1 TGA Parameters Over 72 Hours

The analysis of TGA parameters over 72 hours will be performed on the PKFAS.

TGA parameters will be plotted against time for each subject. In addition, TGA parameters will be summarized using descriptive statistics at each time point.

11.2 TGA Parameters Pre- and Post- Infusion

Analysis of TGA parameters pre- and post- infusion will be performed on the FAS.

TGA parameters will be summarized using descriptive statistics for exposure day 1 (only applicable for newly recruited subjects) as well as for end of study.

In addition, percent changes from pre-infusion time-point will be summarized for exposure day 1 as well as for end of study.
The percent change in TGA parameters will be calculated as:
((tga2-tga1)/tga1)*100,
where tga1 denotes the TGA value at the pre-infusion time-point and tg2 denotes the post-infusion TGA value.

These tables will be created for the on-demand treatment only (i.e. subjects who received on-demand treatment exclusively over the whole study period), for the overall prophylaxis (combined standard, modified and PK-tailored prophylaxis) only, for subjects who received on-demand treatment and any prophylaxis treatment (i.e. subjects who switched during the study) as well as for all treatment regimens together.

Additionally, percent changes from exposure day 1 to end of study will be summarized for newly recruited subjects.

The association of pre-infusion TGA parameters with pre-infusion FIX activity level during prophylaxis will be explored. Scatterplots of pre-infusion TGA parameters against pre-infusion FIX level will be presented for each time point.

In addition, the median pre-infusion TGA parameter against median FIX level for each subject will be presented if pre-infusion values of FIX level and TGA parameters are similar across all time-points. To determine the suitability of this analysis, a plot of individual and median pre-infusion TGA parameter values by subject will be provided. A similar plot will also be produced for pre-infusion FIX activity level at the corresponding time-points.

The association of pre-infusion TGA parameters with spontaneous bleeds during prophylaxis will be explored. This will be done using box plots of the pre-infusion TGA parameter values for subjects who did and who did not experience one or more spontaneous bleeds within 4 weeks after the corresponding pre-infusion TGA sample.

12. ANALYSIS SOFTWARE

All data processing, summarization, and analyses will utilize SAS® software package, Version 9.3 and WinNonlin® Version 6.2, or higher. If the use of other software is warranted the final statistical report will detail what software was used.

13. REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	26 Jul 2017	New Document
2.0	27 Sep 2017	Section 6.6: Updated denominator for clarification and deleted compliance assessment regarding frequencies for modified prophylaxis since definition how data should have been captured was given insufficiently. Section 9.1 and 11.2: IR and TGA will be summarized for baseline and end of study only rather than for all available time points. Minor updates for clarification throughout the whole document.