STATISTICAL ANALYSIS PLAN

NCT Number: NCT03565237

Study Title: Phase IV Multi-Center, Prospective, Interventional, Post-Marketing Study in Hemophilia B Patients in India Receiving RIXUBIS as On-demand or Prophylaxis Under Standard Clinical Practice

Study Number: 251602

SAP Version and Date:

Version 2.0: 29 September 2021

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Statistical Analysis Plan

RIXUBIS Coagulation Factor IX (Recombinant)

Phase IV

PHASE IV MULTI-CENTER, PROSPECTIVE, INTERVENTIONAL, POST-MARKETING STUDY IN HEMOPHILIA B PATIENTS IN INDIA RECEIVING RIXUBIS AS ON-DEMAND OR PROPHYLAXIS UNDER STANDARD CLINICAL PRACTICE

Protocol Identifier: 251602

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Confidentiality Statement

VERSION HISTORY

Version	Issue Date	Summary of Changes
0.1	23 Aug 2019	New Document
0.2	30 Sep 2019	Changes made to address Sponsor's comments in SAP (Text+ TLFs Shells) Draft 0.1 (dated, 23 Aug 2019)
0.3	08 Nov 2019	Changes made to address Sponsor's comments in SAP (Text+ TLFs Shells) Draft 0.2 (dated, 30 Sep 2019)
1.0	22 Nov 2019	Final Version
2.0	28 Sep 2021	Changes made to align with the Dry Run analysis: - Updated section 9.2 for the analysis window - Updated sections 6.1 and 9.3 and for the analysis of Annualized bleeding rate (ABR) - Updated section 7.3.3 for the analysis of FIX Nijmegen - Updated section 5.11 for the analysis of Covid-19 related protocol deviation

APPROVAL SIGNATURES

Study Title: Phase IV Multi-center, Prospective, Interventional, Post-marketing Study in Hemophilia B Patients in India receiving RIXUBIS as On-demand or Prophylaxis Under Standard Clinical Practice

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABR	Annualized Bleeding Rate
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CRF	Case Report Form
CRP	C-Reactive Protein
CTMS	Clinical Trial Management System
eCRF	Electronic Case Report Form
EFAS	Effectiveness Full Analysis Set
FIX	Factor IX
ICF	Informed Consent Form
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IR	Incremental Recovery
MCV	Mean Corpuscular Volume
MCHC	Mean Corpuscular Hemoglobin Concentration
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
PT	Preferred Term
PTP	Previously Treated Patients
Q1	25^{th} percentile
Q3	75^{th} percentile
SAE	Serious Adverse Event

Abbreviation	Definition
SAS	Safety Analysis Set
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WFH	World Federation of Hemophilia
WHO-DD	World Health Organization - Drug Dictionary

1. INTRODUCTION

This statistical analysis plan provides a technical and detailed elaboration of the statistical analyses of safety and efficacy data as described in the final study protocol Amendment 2, dated 27 Sep 2017[1] and Case Report Form (CRF) version 6.0, dated 20 Jul 2021. Specifications for tables, figures, and listings are contained in a separate document.

The purpose of the study is to characterize the safety and efficacy of RIXUBIS when used under standard clinical practice in hemophilia B previously treated patients (PTPs) in India.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of the study is to assess the safety of RIXUBIS based on serious adverse events (SAEs) [including factor IX (FIX) inhibitors].

2.1.2 Secondary Objectives

2.1.2.1 Safety

- To determine the safety of RIXUBIS based on adverse events (AEs)
- To determine the safety of RIXUBIS based on changes in laboratory parameters
- To determine the immunogenicity of RIXUBIS (excluding FIX inhibitors)

2.1.2.2 Efficacy

- To assess the efficacy of prophylactic treatment with RIXUBIS
- To assess the efficacy of RIXUBIS in the control of bleeding episodes

2.1.3 Exploratory Objective(s)

Not applicable

2.2 Endpoints

2.2.1 Primary Endpoint

The primary outcome measure is incidence of SAEs (including FIX inhibitors) possibly or probably related to RIXUBIS.

2.2.2 Secondary Endpoints

2.2.2.1 Safety Endpoints

- Incidence of AEs possibly or probably related to RIXUBIS
- Clinically significant changes in clinical laboratory parameters (hematology and clinical chemistry)
- Incidence of binding immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies to FIX
- Incidence of antibodies to Chinese hamster ovary (CHO) proteins and rFurin

2.2.2.2 Efficacy Endpoints

- Annualized bleeding rate (ABR) with prophylactic use of RIXUBIS
- Rate of success of RIXUBIS for the treatment of bleeding episodes

3. STUDY DESIGN

3.1 General Description

This is a Phase IV multi-center, prospective, interventional, post-marketing study in hemophilia B PTPs in India receiving RIXUBIS under standard clinical practice. The physician is expected to follow standard clinical practice. The safety and efficacy of RIXUBIS under standard clinical practice will be evaluated in a total of 25 evaluable hemophilia B subjects. All study subjects will be included in the assessments of safety and hemostatic effectiveness.

Elective surgeries/procedures are not allowed in this study. Subjects who undergo emergency surgery/procedure during the study will be withdrawn from the study.

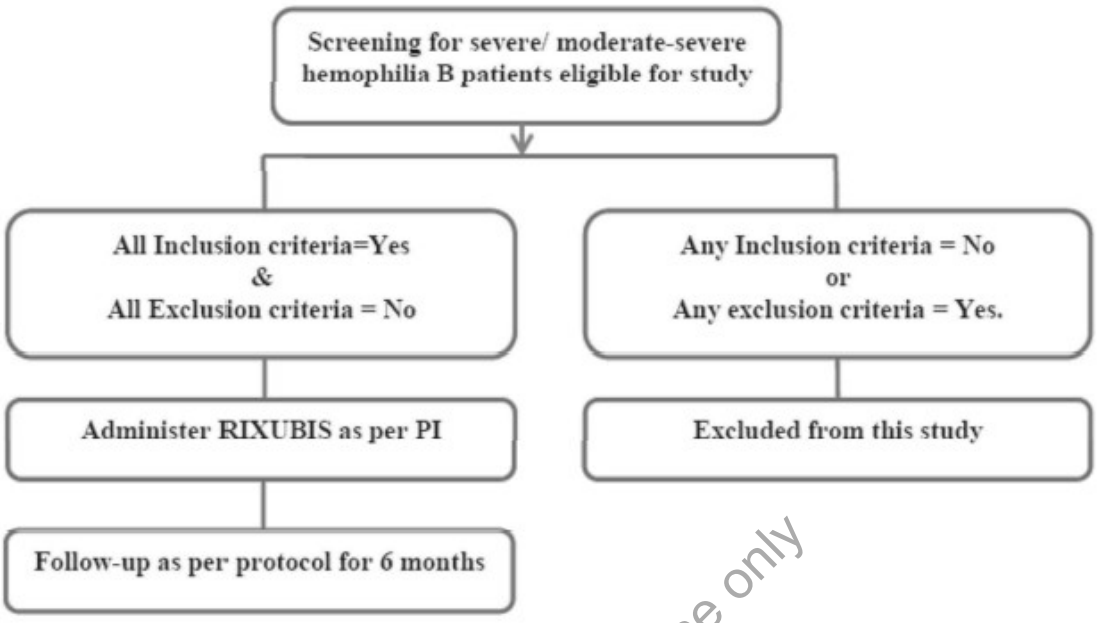
For the purpose of this study, subjects will be defined as PTPs.

The investigator will choose the appropriate RIXUBIS treatment regimen (on-demand or prophylaxis) for the subjects in this study.

The sponsor will bear the cost of RIXUBIS treatment during the study.

The overall study design is illustrated in Figure 1.

Figure 1: Study Design



PI = Principal Investigator

3.2 Randomization

There is no randomization for this study. This is a multi-center, open-label, prospective, interventional, post-marketing Phase IV study in hemophilia B PTPs in India receiving RIXUBIS under standard clinical practice. The physician is expected to follow standard clinical practice.

3.3 Blinding

Not applicable

3.4 Sample Size and Power Considerations

Based on data from the World Federation of Hemophilia (WFH) from 1998-2006,[2] the mean prevalence of hemophilia B in India was 0.19 per 100,000 males. In the WFH Report on the Annual Global Survey 2014,[3] there were a total of 14,450 cases of hemophilia and 2,281 confirmed cases of hemophilia B in India in 2014. Due to the low prevalence of hemophilia B and difficulty to identify patients switching from current therapy, the sample size is relatively low, and it is estimated as 25 subjects to be recruited for this study.

4. STATISTICAL ANALYSIS SETS

4.1 Screened Set

The Screened Set will consist of all subjects who have signed informed consent. This set will be used only to report subject's disposition.

4.2 Effectiveness Full Analysis Set (EFAS)

The EFAS will be comprised of all subjects for whom all inclusion and none of the exclusion criteria are met (enrolled subjects). This dataset will be used for the efficacy analyses.

4.3 Safety Analysis Set (SAS)

All enrolled subjects having received RIXUBIS at any time during the study will be included in the SAS.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

A listing of all screen failures (i.e. subjects who did not meet the study eligibility criteria) will be presented along with reasons for screen failures.

The number and percentage of subjects who will be included in each defined analysis set (i.e. Screened Set, EFAS and SAS) will be summarized overall. The number and percentage of subjects who completed the study, discontinued from the study and the reason for discontinuation (as recorded on the *End of Study* page of the electronic CRF [eCRF]) will be summarized overall.

A listing of all subjects enrolled in the study will present disposition information in EFAS, such information includes: date of informed consent, date of first and last dose of RIXUBIS, date of study completion/termination, primary reason for end of study, any prior participation in another Baxalta study in this program, or, a prior participation in this study (if known and available).

The number of subjects enrolled and completed the study will be tabulated by site for EFAS. In addition, the duration of enrollment, in days, will be summarized for each site and overall. Duration of enrollment will be calculated as: study completion/termination date at that site - date of informed consent for any subject at that site + 1.

5.2 Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented overall for the EFAS and SAS. Demographic and baseline characteristics will be listed for the EFAS.

The following demographic characteristics from the *Demographics* page of the eCRF will be summarized in the following order in the tables age (years), age group category 1 (<12 years and ≥12 years), age group category 2 (<6 years, ≥6 to <12 years, ≥12 to <18 years and ≥18 years), gender, child-bearing potential, ethnicity and race.

Additional baseline characteristics will also be summarized, as following: weight (kg), height (cm) and Body Mass Index (BMI) (kg/m^2) *[Vital Signs eCRF and calculated BMI (derivation follows below)]*.

BMI will be derived (accurately to 1 decimal place) from the eCRF height and weight as follows for presentation in summaries and listings:

BMI (kg/m^2) = weight (kg) / (height $(m)^2$)

5.3 Medical History

Medical history will be collected at the Screening Visit on the *Medical History* eCRF. The subject's medical history will be described for the following body systems, including severity or surgery and start and end dates if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/ lymphatic; dermatological and genitourinary.

These data will be summarized overall for subjects in the EFAS. Listings will be provided using the EFAS.

5.3.1 Hemophilia B History

Hemophilia B history such as: thromboembolism, allergic reactions, inhibitors to FIX and family history of inhibitors to FIX, will be summarized overall for subjects in the EFAS.

The age at diagnosis of hemophilia B, in years, will be derived from eCRF date of birth and date of diagnosis of hemophilia B as follows, for presentation in summaries and listings:

Age at diagnosis of hemophilia B (years) = (Date of hemophilia B diagnosis - Date of birth + 1) / 365.25.

The time since diagnosis of hemophilia B, in years, will be derived (accurately to 1 decimal place) from eCRF date of informed consent form (ICF) signed and date of diagnosis of hemophilia B as follows, for presentation in summaries and listings:

Time since diagnosis of hemophilia B (years) = (ICF date - Date of hemophilia B diagnosis + 1) / 365.25.

Rules how to handle missing dates are described in detail in Section 9.5. Listings will be provided using the EFAS.

5.3.2 Hemophilia B Treatment History

Average ABR based on previous 3-6 months (bleeds per year) and any hemophilia product usage for 6 months prior to screening will be summarized overall for subjects in the EFAS. Counts and percentages of subjects by FIX product and manufacturer name, FIX product status and treatment type will be provided. For subjects on FIX prophylaxis treatment: dosage per infusion (IU/kg), frequency (times per week) and duration of prophylaxis treatment (in months) will be summarized. For subjects on FIX on-demand treatment: average dose required to treat bleed (IU/kg), estimated average number of infusions for each bleeding episode, usual response to treatment ("Excellent", "Good", "Moderate", "None" or "Unknown") and duration of on-demand treatment (in months) will be summarized.

The duration of treatment (prophylaxis or on-demand), in months, will be derived from *Hemophilia B Treatment History* eCRF therapy start date and end date, as follows, for presentation in summaries and listings:

Duration of prophylaxis treatment (months) = (Prophylaxis End Date – Prophylaxis Start Date + 1) / 30.4375.

Duration of on-demand treatment (months) = (On-demand End Date – On-demand Start Date + 1) / 30.4375.

Rules how to handle missing dates are described in detail in Section 9.5. Listings will be provided using the EFAS.

5.4 Bleeding Episodes

Subject's bleeding episodes will include all bleeding episodes during the study. The data will be recorded on the *Bleeding Episode* eCRF. Variables related to the bleeding episodes will include: the number of unique bleeds, location, type and severity of bleeds, cause and severity of the bleeding episode, treatment with RIXUBIS required (yes, no), the subject efficacy rating for bleeding episode (when RIXUBIS was infused) and investigator's efficacy rating (when not in agreement with the efficacy rating provided by the subject/care-giver) any hemostatic product other than RIXUBIS and any analgesic received to treat the bleeding.

Bleeding episodes will be summarized overall and listed for the EFAS.

5.5 Prophylaxis Efficacy Rating

Prophylaxis efficacy rating will be summarized for subjects receiving prophylaxis treatment by scheduled visits (Visit 1, Visit 2 and End of Treatment Visit), as well as for unscheduled visits, for EFAS. Listings will be provided using the EFAS.

5.6 Incremental Recovery

Factor IX levels to determine incremental recovery (IR) for on-demand dosing, additionally could also be assessed at baseline visit. For IR determination, a pre-infusion blood draw will be made within 30 minutes of infusion, followed by a post-infusion blood draw at 30 ± 5 minutes.

The infusion information and the IR will be summarized for all subjects in EFAS with available data. Descriptive statistics will be presented to describe the planned dose (IU/kg), total units infused (IU), total number of lots and vials, FIX concertation value at pre-infusion (IU/dl) and post-infusion (IU/dl) and IR. The number and percentage of subjects, with infusion for determination of IR interrupted (and reason of interruption), re-started and completed, will also be presented.

Listings with all assessments will be provided using EFAS.

5.7 Prior and Concomitant Medications

Prior and concomitant medications will be coded to a preferred term (PT) using the World Health Organization Drug Dictionary (WHO-DD) – Global B3 or newer, dated September 2019.

Prior medications are defined as any medication which has an end date prior to the date of the first dose of RIXUBIS. All medications taken within 3 months before providing informed consent until study completion/termination will be recorded on the *Concomitant Medications* eCRF.

Concomitant medications are defined as any medication with a start date prior to the date of the first dose of RIXUBIS and continuing after the first dose of RIXUBIS, or, with a start date between the dates of the first and last doses of RIXUBIS, inclusive.

Prior and concomitant medication usage will be summarized overall by the number and proportion of subjects who used each medication, as well as the number of administrations, by PT, in the EFAS. Multiple medication usage by a subject in the same category will be counted only once. All prior and concomitant medications will be listed for the EFAS.

5.8 Prior and Concomitant Non-Drug Therapies and Procedures

Prior and concomitant non-drug therapies and procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 or newer.

Prior non-drug therapies and procedures are defined as any non-drug therapy or procedure which has an end date prior to the date of the first dose of RIXUBIS.

All non-drug therapies received within 3 months before providing informed consent until completion/termination will be recorded on the *Non-Drug Therapy* eCRF.

Concomitant non-drug therapy is defined as any non-drug therapy with a start date prior to the date of the first dose of RIXUBIS and continuing after the first dose of RIXUBIS, or, with a start date between the dates of the first and last doses of RIXUBIS, inclusive. Concomitant procedure is defined as any procedure with a start date between the dates of the first and last doses of RIXUBIS, inclusive. Any non-drug therapy/procedure with a start date after the date of the last dose of RIXUBIS will not be considered a concomitant non-therapy/procedure.

Prior or concomitant non-therapies and procedures will be summarized overall by the number and proportion of subjects who used each non-drug therapy or procedure, as well as number of treatments, within each PT, in the EFAS. Multiple non-drug therapy or procedure by a subject in the same category will be counted only once. All prior and concomitant non-therapies and procedures will be listed for the EFAS.

5.9 Exposure to RIXUBIS

A 6-month treatment period is deemed adequate for follow-up as most subjects on prophylaxis will receive RIXUBIS twice weekly equaling 52 doses during the follow-up period.

Exposure to RIXUBIS, for the SAS, will be summarized in terms of treatment duration (in days) respectively for: prophylaxis, to treat bleeding and to maintain hemostasis which is calculated as the number of days from the date of first dose of RIXUBIS taken to the date of the last dose of RIXUBIS taken, inclusively and will be derived from the *RIXUBIS Treatment* eCRF first infusion date and last infusion date, as follows, for presentation in summaries:

RIXUBIS treatment duration for prophylaxis (days):

The treatment duration for prophylaxis will only be calculated in case a subject was on RIXUBIS prophylaxis treatment for at least 3 months[4] (treatment period for surgery and bleeding period are not accounted).

The start date of the **prophylaxis** treatment can be one of the following:

- If a patient was assigned to prophylaxis regimen, the start date will be the first "Infusion Date" with infusion reason "Prophylaxis" after the prophylaxis treatment assignment, in the *RIXUBIS Treatment Log* eCRF page.
- If a patient changed to a new prophylaxis regimen (e.g. change due to bleeding), the start date will be the treatment "Infusion Date", in the *RIXUBIS Treatment Log* eCRF page.

The end date of the **prophylaxis** treatment can be one of the following:

- If a subject did not change from prophylaxis to on-demand regimen then:
  - If a subject does not have a bleeding, the end date will be the last "Infusion Date", in the *RIXUBIS Treatment Log* eCRF page before the "Completion/Termination Date", in the *End of Study* eCRF page (including surgery).
  - If a subject has a bleeding, the end date, for the treatment interruption, will be the day before the "Date of Bleeding Onset", of the first bleeding, in the *Bleeding Episode Log* eCRF page.
- If a subject changed the prophylaxis regimen, since the last visit:
  - The end date will be the last "Infusion Date", in the *RIXUBIS Treatment Log* eCRF page before the "Date when the new regimen became effective since last visit", in the *Prophylaxis Efficacy Rating* eCRF page.

According to the rules above defined for the start and end dates of **prophylaxis** treatment, the RIXUBIS treatment duration for prophylaxis, in days, will be calculated as the summarization of all RIXUBIS prophylaxis regimen durations during the study period, where each prophylaxis duration is defined as the time from the start date of RIXUBIS prophylaxis regimen to the end date of RIXUBIS prophylaxis regimen, on a given period, and will be derived as follows:

RIXUBIS treatment duration for prophylaxis (days) = SUM (end date of RIXUBIS prophylaxis regimen on the i^{th} period – start date of RIXUBIS prophylaxis regimen on the i^{th} -period + 1),

where i= 1; n is the number of periods where RIXUBIS treatment with prophylaxis was given before a bleeding, change of prophylaxis regimen, or end of study.

RIXUBIS treatment duration to treat bleeding (days):

The following start and end dates will be used to calculate the RIXUBIS treatment duration to treat bleeding episodes:

If the reason for RIXUBIS is **to treat bleeding episodes**:

- The start date to treat a bleeding episode will be the "Infusion Date", in the *RIXUBIS Treatment Log* eCRF page
- The end date will be the "Date of Bleeding Resolution", in the *Bleeding Episode Log* eCRF page

According to the rules above defined for the start and end dates **to treat bleeding episodes,** the RIXUBIS treatment duration to treat bleeding episodes will be calculated as the summarization of all durations of RIXUBIS treatment to treat bleeding episodes during the study period, where each treatment duration is defined as the time from the start date of RIXUBIS treatment for a bleeding episode to the end of RIXUBIS treatment for the bleeding episode, on a given period, and will be derived as follows:

RIXUBIS treatment duration to treat bleeding = SUM (end date of RIXUBIS treatment to treat bleeding on the i^{th} period – start date of RIXUBIS treatment to treat bleeding on the i^{th} period + 1),

where i= 1;n is the number of periods where RIXUBIS treatment to treat bleeding was given.

RIXUBIS treatment duration to maintain hemostasis (days):

The following start and end dates will be used to calculate the RIXUBIS treatment duration to maintain hemostasis:

If the reason for RIXUBIS is **to maintain hemostasis**:

- The start date will be the "Infusion Date", in the *RIXUBIS Treatment Log* eCRF page.
- The end date will be the "Date of Bleeding Resolution", in the *Bleeding Episode Log* eCRF page.

According to the rules above defined for the start and end dates **to maintain hemostasis,** the RIXUBIS treatment duration to maintain hemostasis will be calculated as the summarization of all durations of RIXUBIS treatment administered to maintain hemostasis during the study period, where each treatment duration is defined as the time from the start date of RIXUBIS treatment to maintain hemostasis to the end of RIXUBIS treatment to maintain hemostasis, on a given period, and will be derived as follows:

RIXUBIS treatment duration to maintain hemostasis = SUM (end date of RIXUBIS treatment to maintain hemostasis on the i^{th} period – start date of RIXUBIS treatment to maintain hemostasis on the i^{th} period +1)

where i= 1;n is the number of periods where RIXUBIS treatment to maintain hemostasis was given

Additionally, the following quantities will also be summarized overall to describe the exposure to RIXUBIS:

- The total number of infusions per subject
- Total number of infusions per subject, by reason for infusion (prophylaxis, to treat bleeding, to maintain hemostasis)

A listing for RIXUBIS treatment will be created for SAS, by subject number and date of dose administration.

5.10 Measurements of RIXUBIS Compliance

Not applicable

5.11 Protocol Deviations

Protocol deviations will be recorded in the IQVIA Clinical Trial Management System (CTMS). The IQVIA/Baxalta will classify major and minor protocol deviations per the agreed protocol deviation management plan. The Baxalta study team will review the protocol deviations and their classification throughout the study and before final database lock.

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

- Concomitant medication criteria
- Laboratory assessment criteria
- Study procedures criteria
- Serious AE criteria
- Visit schedule criteria
- Investigational product compliance
- Effectiveness criteria

- Administrative criteria
- Source document criteria
- Regulatory or ethics approval criteria
- Covid-19 related criteria
- Other criteria.

Confirmed major and minor protocol deviations will be documented in the protocol deviation tracker for the study. Major/minor protocol deviations will be summarized overall by category for the EFAS. Major/minor protocol deviations will be listed for the EFAS.

6. EFFICACY ANALYSES

All efficacy analyses will be based on the EFAS unless stated otherwise.

Baseline for all efficacy variables is defined as the last observed value for the efficacy assessment prior to taking the first dose of RIXUBIS.

No statistical testing is planned.

6.1 Analyses of Secondary Efficacy Endpoints

In general, the secondary efficacy endpoints will be summarized overall and by RIXUBIS treatment regimen (on-demand or prophylaxis).

The secondary efficacy endpoints are the following:

- The ABR with prophylactic use of RIXUBIS.

  ABR will be summarized, considering the number of unique bleeding episodes (considering zero as a possible number of unique bleeds) per subject, in subjects on prophylaxis treatment for at least 3 months[4], as derived in Section 9.3. All subjects on prophylaxis treatment for at least 3 months will be included in the summary of ABR.

  Note that, the treatment duration for prophylaxis will not consider treatment interruptions.

- The rate of success of RIXUBIS for treatment of bleeding episodes, on-demand use, as derived in Section 9.3.

  For the rate of success of RIXUBIS for treatment of bleeding episodes, 95% Confidence intervals (CIs) will be calculated using the exact Binomial CI (Clopper-Pearson method[5]).

Summary tables for rate of success of RIXUBIS for treatment of bleeding episodes and ABR as on prophylaxis, will also be presented by the location of bleed (skin, venipuncture site, muscle, soft tissue, mucosal, joint, body cavity, hematuria, genitourinary, gastrointestinal, intracranial, other), cause of bleed (spontaneous, injury, unknown) and severity of bleed (minor, moderate, major, life/limb threatening).

6.2 Multiplicity Adjustment

Not applicable

7. SAFETY ANALYSIS

The safety analysis will be performed using the SAS. Safety variables include AEs, clinical laboratory variables and vital signs.

7.1 Adverse Events

AEs will be coded using the MedDRA dictionary, Version 22.1 or newer and grouped by System organ class (SOC) and PT.

A treatment-emergent AE (TEAE) is defined as any event non-present prior to the initiation of RIXUBIS or any event already present that worsens in either intensity or frequency following exposure to RIXUBIS.

An overall summary of the number of subjects with AEs and TEAEs as well as the number of events will be presented, including the number and percentage of subjects with any TEAEs, TEAEs related ("possibly related" or "probably related") to RIXUBIS, serious TEAEs, related serious TEAEs, TEAEs leading to discontinuation from study and serious TEAEs leading to death.

The number and percentage of subjects reporting TEAEs, as well as the number of events, overall and by each RIXUBIS treatment regimen (on-demand or prophylaxis) will be tabulated by SOC and PT, and maximum severity. If more than 1 AE occurs with the same PT for the same subject, then the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to RIXUBIS. Presentation by SOC and PT will present SOC sorted by descending frequency and then by descending frequency of PT within SOC.

TEAEs, possibly or probably drug related TEAEs, serious TEAEs, related serious TEAEs, TEAEs leading to discontinuation from study and serious TEAEs leading to death, will be summarized by SOC and PT, overall and by RIXUBIS treatment regimen (on-demand or prophylaxis). A Listing for AEs will be presented, and TEAEs will be flagged.

7.2 Analysis of Primary Safety Endpoints

For the analysis of primary safety endpoint, the number of possibly or probably related SAEs (including FIX inhibitors) as well as the number and percentage of subjects with possibly or probably related SAEs (including FIX inhibitors) that occurred during or after first RIXUBIS infusion (serious TEAEs), will be summarized by SOC and PT, overall and by RIXUBIS treatment regimen (on-demand or prophylaxis).

7.3 Analyses of Secondary Safety Endpoints

7.3.1 Related TEAEs

The number of possibly or probably related AEs (including FIX inhibitors) as well as the number and percentage of subjects with possibly or probably related AEs (including FIX inhibitors) that occurred during or after first RIXUBIS infusion (TEAEs), will be summarized by SOC and PT, overall and by RIXUBIS treatment regimen (on-demand or prophylaxis).

7.3.2 Clinical Laboratory Data

Descriptive statistics for clinical laboratory values as obtained from the central laboratory (in SI units) and changes from baseline at each planned assessment time point, as well as, shift tables to each planned visit for quantitative variables will be presented overall and by RIXUBIS treatment regimen (on-demand or prophylaxis) for the following laboratory variables:

Hematology	Complete blood count [hemoglobin, hematocrit, erythrocytes (i.e., red blood cell count), and leukocytes (i.e., white blood cell count)] with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and platelet count
Biochemistry	Sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate transaminase (AST), total bilirubin, alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatine and glucose
Urinalysis	Urine dipstick protein

Shift tables based on evaluation against the reference range (low, normal, high) at baseline and post-baseline assessment time points will be presented for the same list of planned parameters, overall and by RIXUBIS treatment regimen (on-demand or prophylaxis). The number and percentage of subjects in each post-baseline category will be based on the number of SAS subjects who had both baseline and post-baseline data for a parameter within a specified timepoint and RIXUBIS treatment regimen (on-demand or prophylaxis).

All clinical laboratory data will be listed for the SAS. An additional supportive listing of subjects with post-baseline abnormal clinically significant values will be provided including the subject number, site, baseline, and post-baseline abnormal clinically significant values.

Laboratory values will be evaluated for clinical significance by the investigator. Clinically significant results may be recorded as AEs, at the discretion of the investigator. The number and percentage of subjects with clinically significant abnormal values on any parameter and by parameter will be tabulated for the study overall (i.e. at any time during the treatment period), at each planned timepoint for overall. All available data from both scheduled and unscheduled assessments will be used. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment in a specified analysis window (See Section 9.2). The numerator will be the total number of subjects with at least 1 clinically significant post-baseline laboratory value in the specified analysis window.

7.3.3 Immunogenicity

Subjects developing binding IgG or IgM antibodies (i.e. with a positive result) to FIX, or antibodies to CHO proteins, or rFurin will be summarized in terms of counts and percentages at each study timepoint.

For FIX Nijmegen, negative result will be defined as any value <0.6 Bethesda Unit.

Results will be presented overall and by RIXUBIS treatment regimen (on-demand or prophylaxis). All sample results will be listed.

7.3.4 Pregnancy Notification

The number of pregnancies of the subject (or subject's partner) during the clinical study will be listed for the EFAS and SAS.

7.4 Vital Signs

Vital signs will be assessed pre- and post-infusion at each visit. Vital signs will include body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (cm) and body weight (kg) will also be collected.

Descriptive statistics for vital signs as reported on the *Vital Signs* eCRFs at each planned timepoint will be presented overall and by RIXUBIS treatment regimen (on-demand or prophylaxis), as well as vital signs percentage of change from baseline.

All vital signs data will be listed for the SAS.

7.5 Other Safety Data

No other safety assessments/variables are planned for this study.

8. INTERIM ANALYSIS/ DATA MONITORING (REVIEW) COMMITTEE

No formal interim analysis will be performed.

9. DATA HANDLING CONVENTIONS

9.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation (SD), interquartile ranges (Q1, Q3), minimum, maximum. For measures of median and mean, 1 decimal place beyond those used will be used for the measurement. For measures of SD, 2 decimal places beyond those used will be used for the measurement. Measures of minimum and maximum values will use the same number of decimal places as those used for the measurement.

Categorical and count variables will be summarized by the number of subjects (n) and the percent (%) of subjects in each category. Percentages will be calculated based on available (non-missing) data within the analysis set. Percentages will be presented with one decimal place, except when the percentage equals exactly 100 where it shall be displayed as an integer (100). For zero, only count and no percentage will be displayed.

CIs will be presented as: xx.x, xx.x

Table completely empty will be prepared with the respective title and footnote, but with the text "- No observations -" in the body of the output.

All subject data that are collected during this study will be disclosed on listings. Listings will be sorted by subject number, unless otherwise specified.

9.2 Definition of Visit Windows

Assessments will be assigned to visits based on the information reported in the completed eCRF page at each planned visit.

9.3 Derived Efficacy Endpoints

The ABR for each subject, will be defined as the total number of unique bleeding episodes by subject reported during RIXUBIS treatment for prophylaxis, divided by the RIXUBIS treatment duration for prophylaxis and multiplied by 365.25.

The ABR will only be calculated in case a subject was on RIXUBIS prophylaxis treatment for at least 3 months[4]. The ABR will be derived as follows:

ABR with prophylaxis = number of unique bleeds during prophylaxis / RIXUBIS treatment duration for prophylaxis / 365.25

The ABR numerator is the number of unique bleeds during prophylaxis, calculated as the sum of bleeds that occurred during prophylaxis treatment. Zero is considered as a possible number of unique bleeds. The unique bleeds are defined as follows:

- If a bleed occurs during prophylaxis treatment it should count as a unique bleed on prophylaxis treatment
- Subsequent bleedings that occur after stop of prophylaxis treatment, or when the subject change treatment, or before the next prophylaxis treatment will not count as a unique bleed during prophylaxis treatment.

The ABR denominator is the RIXUBIS treatment duration for prophylaxis, as defined in Section 5.9. The formula above will be presented for subjects receiving RIXUBIS treatment regimen as on prophylaxis for at least 3 months.

The success of RIXUBIS for the treatment of bleeding episodes is defined by grouping the categories of "Excellent"/"Good" of the corresponding hemostatic effectiveness ratings of a 4-point Likert scale ("Excellent", "Good", "Moderate" and "None") by the subjects/care-givers (subjects <12 years: care-giver, subjects ≥ 12 years: self-assessment) for treatments given at home, or by the investigator for treatments given in the hospital/clinic.

In cases where there is any discrepancy between assessments made by subjects (or the subject's legal representative) and the investigator, assessment made by the investigator shall supersede and be considered the final assessment.

The rate of success of RIXUBIS for treatment of bleeding episodes will be defined as:

$$Rate\ of\ success\ of\ Rixubis\ = \frac{Number\ of\ successful\ bleeding\ episodes}{Total\ number\ of\ bleeding\ episodes\ where\ the\ treatment\ of\ the\ bleeding\ was\ rated}\ x\ 100$$

9.4 Unscheduled Assessments of Safety Parameters

Unscheduled assessments (i.e., not done at a planned visit) will not be used for time point specific summaries but will be used in tabulation of clinically significant abnormal values.

All assessments will be presented in the data listings.

9.5 Handling of Missing, Unused, and Spurious Data

All data will be evaluated as observed. A subject who withdraws prior to the last planned observation in study period will be included in the analyses up to the time of withdrawal.

However, imputation rules for the below dates when they are partial or complete missing will be applied:

- Date of hemophilia B diagnosis:
    - if the day is missing, the 1st day of the month will be imputed
    - if the month are missing, the June month will be imputed
    - if both, day, and month are missing the 30th June will be imputed
    - if the date is completely missing, no imputation will be performed.

- Prophylaxis and/or on-demand treatment start date, in the hemophilia B Treatment History eCRF page
    - if the day is missing, the 1st day of the month will be imputed
    - if the month are missing, no imputation will be performed
    - if the date is completely missing, no imputation will be performed.

- Prophylaxis and/or on-demand treatment end date, in the *Hemophilia B Treatment History* eCRF page
    - if the day is missing, the last day of the month will be imputed
    - if the month are missing, no imputation will be performed
    - if the date is completely missing, no imputation will be performed

9.5.1 Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, a character string, such as ">" or "<", is reported for a numerical variable. The appropriately determined coded value will be used in the statistical analysis. However, the actual values as reported in the database will be presented in data listings.

10. ANALYSIS SOFTWARE

Statistical analyses will be performed using SAS® Software, Version 9.4 (SAS Institute Inc., Cary, NC, USA) or newer, on a suitably qualified environment.

11. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

Not applicable

12. REFERENCES

1. Baxalta Protocol 251602: Phase IV multi-center, prospective, interventional, post-marketing study in Hemophilia B patients in India receiving RIXUBIS as on-demand or Prophylaxis under standard clinical practice. Protocol Amendment 2, dated 2017 SEP 27.

2. Stonebraker JS, Bolton-Maggs PHB, Soucie JM, Walker I, Brooker M. A study of variations in the reported haemophilia B prevalence around the world. Haemophilia. 2012;18(3):e91-e94.

3. World Federation of Hemophilia. Report on the Annual Global Survey, 2014: Montreal, Quebec, Canada:2015:54. Web Link: http://www1.wfh.org/publications/files/pdf-1627.pdf

4. Collins, Peter William, Blanchette, V. S., Fischer, K., Bjorkman, S., Oh, M., Fritsch, S., Schroth, P., Spotts, G., Astermark, J. and Ewenstein, B. 2009. Break-through bleeding in relation to predicted factor VIII levels in patients receiving prophylactic treatment for severe hemophilia A. Journal of Thrombosis and Haemostatis 7 (3), pp. 413-420. 10.1111/j.1538-7836.2008.03270.x

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Appendix 1 Schedule of Activities

Schedule of Study Procedures and Assessments

Table A1. Schedule of Study Procedures and Assessments for PTPs[a]

Procedures/ Assessments	ICF Screening Visit	Baseline Visit	Visit 1	Visit 2	Unscheduled Visit(s)[b]	End of Treatment Visit	Study Termination Visit[c]
Time Point	**Up to 45 days prior to Day 0**	**Day 0**	**1 month ± 1 week**	**3 months ± 1 week**		**6 month ± 1 week**	
Informed Consent[d]	X						
Eligibility Criteria	X	X[e]					
Medical History	X						
Bleeding History	X						
Hemophilia B Treatment History	X						
Medications History (other than Hemophilia B)	X						
Physical Exam	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Laboratory assessments[f]	See (Table A2)						
Vital Signs	X	X	X	X	X	X	X
Bleeding Episodes and Their Treatment[g]	X	X	X	X	X	X	X
Review of Subject Diary		X	X	X	X	X	X
Assessment of Hemostatic Effectiveness		X	X	X	X (if applicable)	X	X
RIXUBIS Dispense[h]	X	X	X	X	X	X	X
End of Study Form		X	X	X	X	X	X

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[a] Define as Subject aged ≥ 6 years that has been previously treated with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 150 Eds OR Subject aged < 6 years that has been previously treated with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 50 EDs.
[b] Unscheduled visits could be performed for any reason (bleed management, safety event, etc.) as per Investigators' discretion
[c] Study Termination Visit will be performed only if subject is discontinuing the study or withdrawing from the study without completing the End of Treatment Visit.
[d] Occurs prior to any study-specific procedure.
[e] Same eligibility criteria to be used as Screening.
[f] For laboratory assessments, see Section 20.3 in protocol. At all assessments, subjects must not to be actively bleeding.
[g] To collect information on the type of bleeding episodes (site, severity, duration) and the treatment used for the bleeding episodes (drug, dose, frequency, duration).
[h] RIXUBIS should be dispensed to provide sufficient treatment until at least the next scheduled visit, or as appropriate.

Clinical Laboratory Assessments

Table A2. Schedule of Clinical Laboratory Assessments for PTPs[a]

Procedures/ Assessments	ICF Screening Visit	Baseline Visit	Visit 1	Visit 2	Unscheduled Visit(s)[b]	End of Treatment Visit	Study Termination Visit[c]
Time Point	**Up to 45 days prior to Day 0**	**Day 0**	**1 month ± 1 week**	**3 months ± 1 week**		**6 month ± 1 week**	
Hematology[d]	X				X (optional)	X	X
Clinical chemistry[e]	X				X (optional)	X	X
Urinalysis[f]	X				X (optional)	X	X
FIX Activity	X				X (optional)		
FIX Antigen	X						
FIX Recovery[g]		X (optional)					
Immunology[h]	X	X	X	X	X	X	X

[a] Define as Subject aged ≥ 6 years that has been previously treated with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 150 Eds OR Subject aged < 6 years that has been previously treated with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 50 EDs

[b] Unscheduled visits could be performed for any reason (bleed management, safety event, etc.) as per Investigators' discretion

[c] Study Termination Visit will be performed only if subject is discontinuing the study or withdrawing from the study without completing the End of Treatment Visit

[d] Hematology assessments include: hemoglobin, hematocrit, red blood cell count, and white blood cell count with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and platelet count

[e] Clinical chemistry assessments include: sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, and glucose

[f] Urinalysis assessment include: protein. Urinalysis should also be performed if inhibitors are detected

[g] For assessment of recovery: samples will be taken within 0 5 h before the start of the infusion, and at 0.5 h ± 5 minutes after the infusion

[h] Immunology assessments include: total binding and inhibitory antibodies to FIX, and antibodies to CHO protein and rFurin. If an inhibitory antibody with a Nijmegen titer ≥ 0.6 BU or total binding antibodies with a positive titer of 1:80 is detected, the test will be confirmed in the central laboratory within 2 weeks of study site notification. In either case the following additional tests will be performed: IgA, IgM, IgG subtypes, and hs-CRP; additional markers may be tested if applicable. If an inhibitor is suspected there may be additional testing for lupus anticoagulants/phospholipid antibodies, or FIX antibody testing with a different methodology. If a subject develops a severe allergic reaction or anaphylaxis the following tests will be performed: hs-CRP, CIC-C1q and CIC-C3 for circulating immune complexes, and IgE