CLINICAL STUDY PROTOCOL

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

Protocol Version and Date:

Amendment 2: 27 Sep 2017

Amendment 1: 15 Sep 2016

Original Protocol: 25 Apr 2016

CLINICAL STUDY PROTOCOL

PRODUCT: RIXUBIS Coagulation Factor IX (Recombinant)

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 SHORT TITLE: RIXUBIS INDIA PMC Study

PROTOCOL IDENTIFIER: 251602

CLINICAL TRIAL PHASE IV

AMENDMENT 2: 2017 SEP 27

Replaces: Amendment 1: 2016 SEP 15

ALL VERSIONS:
Amendment 2: 2017 SEP 27
Amendment 1: 2016 SEP 15
Original: 2016 APR 25

OTHER IDs:
NCT Number: pending
EudraCT Number: not applicable
IND NUMBER: not applicable

Study Sponsor(s): **Baxalta Innovations GmbH**
Industriestrasse 67
A-1221 Vienna,
AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD

[redacted]

Baxalta Innovations GmbH

1.2 Study Organization

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

2. SERIOUS ADVERSE EVENT REPORTING

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

ALL SAEs, INCLUDING SUSARs, ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT

Drug Safety contact information: see SAE Report form
Refer to SAE Protocol Sections and the study team roster for further information.

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

- AE, Section 12.1
- SAE, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- Assessment of AEs, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	RIXUBIS
Name(s) of Active Ingredient(s)	Coagulation Factor IX (Recombinant)
CLINICAL CONDITION(S)/INDICATION(S) • Hemophilia B	
PROTOCOL ID	251602
PROTOCOL 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
Short Title	RIXUBIS INDIA PMC Study
STUDY PHASE	Phase 4 (postmarketing)
PLANNED STUDY PERIOD	
Initiation	2018 January 13
Primary Completion	2020 December 27
Study Completion	2020 December 27
Duration	3 years
STUDY OBJECTIVES AND PURPOSE	
Study Purpose 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.	
Primary Objective The primary objective of the study is to assess the safety of RIXUBIS based on SAEs (including FIX inhibitors).	
Secondary Objective(s) **Safety** • To determine the safety of RIXUBIS based on AEs • To determine the safety of RIXUBIS based on changes in laboratory parameters • To determine the immunogenicity of RIXUBIS (excluding FIX inhibitors) **Efficacy** • To assess the efficacy of prophylactic treatment with RIXUBIS • To assess the efficacy of RIXUBIS in the control of bleeding episodes	

STUDY DESIGN	
Study Type/ Classification/ Discipline	Safety and Efficacy
Control Type	No control
Study Indication Type	Treatment
Intervention model	Single-group
Blinding/Masking	Open-label
Study Design	This is a Phase IV multi-center, prospective, interventional, post-marketing study in hemophilia B PTPs in India receiving RIXUBIS under standard clinical practice.
Planned Duration of Subject Participation	Approximately 7-8 months

Primary Outcome Measure

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

Secondary Outcome Measure(s)

Safety

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

Efficacy

- Annualized bleeding rate with prophylactic use of RIXUBIS
- Rate of success of RIXUBIS for treatment of bleeding episodes

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	RIXUBIS Refer to the RIXUBIS India Product Label for further information
SUBJECT SELECTION	
Targeted Accrual	25
Number of Groups/ Arms/Cohorts	1

Inclusion Criteria

1. The subject or legally authorized representative (in case of study participants <18 years of age) gave written informed consent to participate in the study.
2. Subject has hemophilia B.
3. Subject is defined as previously-treated patient (PTP):
   - Subject aged ≥ 6 years that has been previously treated with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 150 EDs.
   - Subject aged < 6 years that has been previously treated with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 50 EDs.
4. Subject has no evidence of a history of FIX inhibitors.
5. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm3, as confirmed by central laboratory at screening.
6. Subject is hepatitis C virus negative (HCV-) by antibody or PCR testing (if positive, antibody titer will be confirmed by PCR), as confirmed by central laboratory at screening; or HCV+ with chronic stable hepatitis.
7. The subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

1. Subject has known hypersensitivity or presence of any contraindication to RIXUBIS or its excipients including hamster protein.
2. Subject has evidence of an ongoing or recent thrombotic disease, fibrinolysis or disseminated intravascular coagulation (DIC).
3. 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.
4. 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.
5. 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.
6. Subject has severe chronic hepatic dysfunction [eg, ≥ 5 times upper limit of normal alanine aminotransferase (ALT), as confirmed by central laboratory at screening, or a documented INR > 1.5].
7. Subject has severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening.
8. Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia B.
9. Subject's platelet count is < 100,000/mL.
10. 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.
11. 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 antiretroviral chemotherapy.

12. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
13. Subject is a family member or employee of the investigator.

STATISTICAL ANALYSIS

Sample Size Calculation

Based on data from the WFH from 1998-2006, the mean prevalence of hemophilia B in India was 0.19 per 100,000 male. In the WFH Report on the Annual Global Survey 2014, 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 in switching patient from current therapy, an estimated study size of 25 subjects will be recruited.

Planned Statistical Analysis

Statistical analysis for this study will be descriptive in nature.

Primary Outcome Measure:

The number of possibly or probably related SAEs (including FIX inhibitors) as well as the number of subjects with possibly or probably related SAEs (including FIX inhibitors) that occurred during or after first RIXUBIS infusion will be summarized.

Secondary Outcome Measures:

Safety:

The number of possibly or probably related adverse events as well as the number of subjects with possibly or probably related adverse events that occurred during or after first RIXUBIS infusion will be summarized.

Shift tables will be presented for the results of clinical laboratory data.

Subjects developing binding IgG or IgM antibodies to FIX or antibodies to CHO proteins or rFurin will be summarized.

Efficacy:

Summary statistics will be provided for the rate of success of RIXUBIS for treatment of bleeding episodes as well as for the annualized bleeding rate (ABR) with prophylactic use of RIXUBIS. These tables will be also presented by bleeding site, cause and severity.

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Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	antibody
ABR	annualized bleed rate
ADE	adverse drug event
ADR	adverse drug reaction
AE	adverse event
Ag	antigen
ALT	alanine aminotransferase (synonymous with SGPT)
ANC	absolute neutrophil count
AST	aspartate aminotransferase (synonymous with SGOT)
BU	Bethesda unit
BUN	blood urea nitrogen
CF	consent form
CFR	Code of Federal Regulations
CSR	clinical study report
CTA	Clinical Trial Agreement
DIC	disseminated intravascular coagulation
DNA	deoxyribonucleic acid
EC	ethics committee
eCRF	electronic case report form
ED	exposure day
EDC	electronic data capture/collection
EDTA	edetic acid (ethylenediaminetetraacetic acid)
ELISA	enzyme-linked immunosorbent assay
EUDRA	European Union Drug Regulatory Authorities
EUDRACT	European Union clinical trials database
FIX	factor IX
GCP	good clinical practice
GmbH	*Gesellschaft mit beschränkter Haftung* − German term for a company that does not trade its shares on the stock market
HA	hemagglutination

Abbreviation	Definition
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
HIV-1, HIV-2 or HIV-1/2	human immunodeficiency virus type 1, type 2, or type 1 & 2
i.v.	intravenous(ly)
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
Ig	immunoglobulin
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IM	intramuscular
IND	Investigational New Drug application (FDA)
INR	international normalized ratio
IP	investigational product
IR	incremental recovery
ITI	immune tolerance induction
IU	international unit(s)
kg	kilogram(s)
L	liter(s)
lb	pound(s)
M	molar
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MD	medical doctor
min	minute(s)

Abbreviation	Definition
Min	minimum
mL	milliliter(s)
mm	millimeter(s)
mmHg	millimeter(s) of mercury
ng	nanogram(s)
nm	nanometer(s)
PASS	Post-Authorization Safety Surveillance
PCR	polymerase chain reaction
Ph Eur	European Pharmacopeia
PMS	postmarketing surveillance
PRO	patient-reported outcome
PTP	previously treated patient
QoL	quality of life
SAE	serious adverse event
SAER	Serious Adverse Event Report
SAP	statistical analysis plan
SAS	Safety Analysis Set
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SIC	subject identification code
SOC	system organ class
SWFI	sterile water for injection
$T_{1/2}$	half-life
U	unit(s)
US	United States
µmol	micromole(s)
µg	microgram(s)

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

RIXUBIS (recombinant coagulation factor IX) is a single-chain purified glycoprotein that has 415 amino acids. It is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell line. RIXUBIS is not derived from human blood or plasma products, and its manufacturer does not include animal or human components. RIXUBIS contains no preservatives. Recombinant coagulation factor IX is a single chain glycoprotein that is a member of the serine protease family of vitamin K-dependent coagulation factors.

Recombinant coagulation factor IX is a recombinant DNA-based protein therapeutic which has structural and functional characteristics comparable to endogenous factor IX. Factor IX is activated by factor VIIa/tissue factor complex in the extrinsic pathway and by factor XIa in the intrinsic coagulation pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. This results ultimately in the conversion of prothrombin to thrombin. Thrombin then converts fibrinogen into fibrin, and a clot can be formed.

6.2 Clinical Condition/Indication

Hemophilia B is an X chromosome-linked recessive congenital disorder of blood coagulation due to decreased levels or complete lack of factor IX and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma.

Hemophilia B affects 1-2 infants per 50,000 male newborns. In patients with hemophilia B, susceptibility to uncontrolled bleeding is influenced by disease severity defined by the baseline plasma factor levels of >5% to <40% (mild), 1% to 5% (moderate), or <1% (severe). Of the patients with hemophilia B, approximately 26% reported to have mild, 38% had moderate and 36% had severe disease.[1]

Replacement FIX therapy increases the plasma level of factor IX, providing a temporary correction of the factor deficiency and the bleeding tendency.

One of the most serious complications of replacement therapy is the development of inhibitory antibodies against the exogenously applied coagulation factor in as many as 20-30% of patients with severe hemophilia A, and in 1-5% of patients with severe hemophilia B. The risk for inhibitor development to FIX depends on a number of factors relating to the characteristics of the patient, including: the causative FIX gene mutations, family history, ethnicity, intensity of treatment, and the early implementation of prophylactic treatment.

A substantial proportion of patients with FIX inhibitors have high responding, high titer inhibitors [>5 Bethesda units (BU)]. Inhibitor development in hemophilia B is associated with the development of anaphylactic reactions. Immune tolerance induction (ITI) is frequently less successful in these patients and subjects may develop a nephrotic syndrome as a result of ITI.

6.3 Population To Be Studied

This study will enroll hemophilia B subjects in India.

According to the World Federation of Hemophilia (WFH) Report on the Annual Global Survey 2014, there were a total of 14,450 cases of hemophilia and 2,281 confirmed cases of hemophilia B in India in 2014.[2] The number of patients with hemophilia B in India who developed inhibitors was not available. Based on data from the WFH from 1998-2006, the mean prevalence of hemophilia B in India was 0.19 per 100,000 males.[3] The India National hemophilia registry (NHR) reports showed 50% of diagnosed hemophilia B patients are on factor IX treatment.

The age distribution of Hemophilia B in India is as follows: 3% between 0-4 years, 14% between 5-13 years, 13% between 14-18 years, 34% between 19-44 years and 7% 45+ years; age was unknown for 29% of patients with hemophilia B.[2]

The total IU of Factor IX in 2014 reported to the WFH was 1,226,400 IU, of which 100% was plasma-derived and 0% was recombinant Factor IX. In 2014, the per capita use of factor IX in India was 0.001 IU per capita. The per capita Factor IX use was consistent from the use reported from 1998-2006 (mean 0.001 IU per capita).[4]
The average Factor IX use per patient with hemophilia B from 1998 to 2006 was 203 IU in India.

6.4 Findings from Nonclinical and Clinical Studies

RIXUBIS is licensed in 18 countries and regions; it is safe and well-tolerated in the treatment of haemophilia B. Detailed summaries of nonclinical and clinical findings can be found in the RIXUBIS Product Label for India and the RIXUBIS Investigator´s Brochure.

The licensure of RIXUBIS was obtained in India based on the efficacy and safety data evaluated in 4 clinical studies: a pivotal trial, a pediatric trial, a surgery trial, and an ongoing continuation study.

No actions relating to safety have been taken by the marketing authorization holder, sponsor, regulatory authorities, and data monitoring committees, or ethics committees thus far on RIXUBIS.

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

RIXUBIS is indicated in adults and children with hemophilia B for the control and prevention of bleeding episodes and routine prophylaxis. There is an identified risk of hypersensitivity reactions [including reactions/antibodies to Chinese Hamster Ovary (CHO) protein] to RIXUBIS. Potential risks include inhibitor formation, lack of effect, thromboembolic events and nephrotic syndrome following attempted immune tolerance induction in haemophila B patients with FIX inhibitors and a history of allergic reactions.

RIXUBIS is therefore not indicated for induction of immune tolerance in patients with Hemophilia B and contraindicated in known hypersensitivity to RIXUBIS or its excipients including CHO protein, disseminated intravascular coagulation (DIC) and signs of fibrinolysis. RIXUBIS treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia.

6.6 Compliance Statement

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

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

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

7.2 Primary Objective

The primary objective of the study is to assess the safety of RIXUBIS based on SAEs (including FIX inhibitors).

7.3 Secondary Objectives

7.3.1 Safety

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

7.3.2 Efficacy

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

8. STUDY DESIGN

8.1 Brief Summary

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 (previously-treated patients) as per Section 9.1.

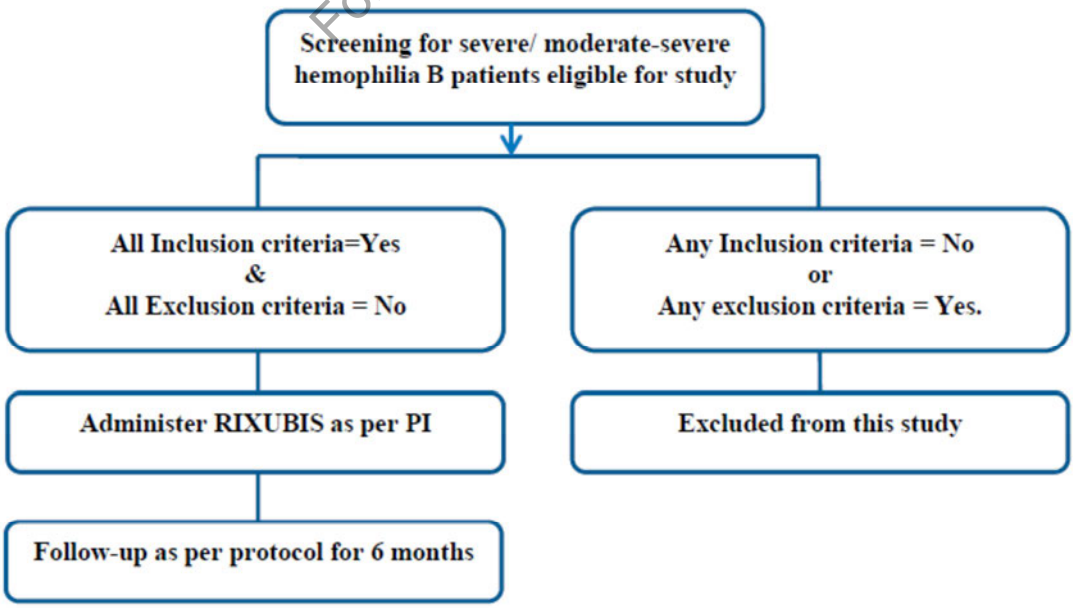
The Investigator will choose the appropriate RIXUBIS treatment regimen (on-demand or prophylaxis) for the subject in this study.

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

8.2 Overall Study Design

The overall study design is illustrated in Figure 1.

Figure 1. Study Design



8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study is 36 months from study initiation (ie, first subject enrolled) to study completion (ie, last subject last visit). The recruitment period is expected to be approximately 30 months.

The follow-up period for each enrolled patient will be up to 6 months from baseline while on treatment. The following visits will be performed:

- Baseline, 1 month, 3 month, and 6 month

A 6 months treatment period is deemed adequate for follow-up as most patients on prophylaxis will receive RIXUBIS twice weekly equaling 52 doses during the follow-up period. Additionally, for the control and prevention of bleeding episodes, patient could receive RIXUBIS for up to 10 days depending on the type of bleeding episode. Given our knowledge of the pharmacokinetics, efficacy and safety profile of RIXUBIS, we believe hemostatic effectiveness can be assessed and any safety issues identified during the 6-month treatment period.

Note: Subjects will be discontinued from the study after they have been in the study for 6 months, irrespective of the RIXUBIS EDs they have received during that 6-month period.

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

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

8.4.2 Secondary Outcome Measures

8.4.2.1 Safety

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

8.4.2.2 Efficacy

- Annualized bleeding rate with prophylactic use of RIXUBIS
- Rate of success of RIXUBIS for treatment of bleeding episodes

8.5 Randomization and Blinding

This is a Phase IV 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.

8.6 Study Stopping Rules

This study will be stopped if the following criterion is met:

1. The sponsor decides to terminate the study for administrative reasons.

8.7 Investigational Product(s)

8.7.1 Packaging, Labeling, and Storage

RIXUBIS is formulated as a sterile, nonpyrogenic, lyophilized powder of concentrated rFIX for intravenous injection and is provided in a single-dose vial labeled with the rFIX activity expressed in IU.

Subjects will use the commercial material employed for the study.

RIXUBIS is infused intravenously after reconstitution with Sterile Water for Injection (SWFI). A single package contains: one vial of lyophilized powder with a nominal potency of 250, 500, 1000, 2000 or 3000 IU/vial; one vial with 5 mL of SWFI; and a needleless transfer device for reconstitution (BAXJECT II). The ancillary package contains: 10, 20, and 30 mL plastic syringes, and a 23-gauge winged infusion set.

Each vial will be labeled with the actual potency in International Units and a Product Label. The Product Label will meet country-specific regulatory label requirements.

For reconstitution instructions, please refer to the RIXUBIS Product Label for India.

Vials from different lots/infusion, preferably not more than two different lots/infusion may be used for the prophylactic or on-demand treatment, however each vial must be reconstituted with its own kit, ie, a separate BAXJECT II must be used for reconstitution of each vial.

RIXUBIS is to be stored at +2° to +8°C (36 to 46°F). Freezing should be avoided to prevent damage to the diluent vial. The reconstituted product should be used immediately, but no longer than 3 hours after reconstitution. Chemical and physical in use stability has been demonstrated for 3 hours at temperatures up to 25°C. Additional shelf-life information can be found in the RIXUBIS Product Label for India.

8.7.2 Administration

Following reconstitution, RIXUBIS should be administered at room temperature and within 3 hours of reconstitution. Plastic syringes provided by the sponsor must be used with this product since proteins such as RIXUBIS tend to stick to the surface of glass syringes. The infusions will be administered by intravenous bolus at a maximum infusion rate of 10 mL/minute. It is recommended that the first dose of RIXUBIS is infused in the clinic.

Additional information can be found in the RIXUBIS Product Label for India.

8.7.3 Description of Treatment

All subjects will receive exclusively RIXUBIS.

The physician is expected to follow standard clinical practice. The treatment with RIXUBIS will be at the discretion of the physician, and will consist of either prophylaxis or on-demand.

Dosing and other additional information can be found in the RIXUBIS Product Label for India.

8.7.3.1 Use of Incremental Recovery (IR) for On-demand Dosing

As discussed in the RIXUBIS Product Label for India, IR is used for the dosing calculation for the on-demand treatment of bleeding episodes. The following guideline will be used for IR determination:

- For PTPs, an IR of 0.7 IU/dL will be used for subjects <12 years and an IR of 0.9 IU/dL will be used for subjects ≥12 years. IR determination could also be performed at baseline as per Section 8.7.3.1.1 but it is optional.

8.7.3.1.1 Determination of IR (Optional)

At baseline, subjects will be infused with 50 ± 5 IU/kg of RIXUBIS. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution. All assessments should be done at least 5 days after the previous dose of

RIXUBIS, and the subject must not actively bleed. For IR determination, a pre-infusion blood draw will be made within 30 minutes of infusion, followed by a post-infusion blood draw at 15-30 minutes.

8.7.4 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. IP(s) must be dispensed only at the study site or other suitable location (e.g. infusion center; home, as applicable per study design). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.8 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

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

For additional information on study documentation and CRFs, see Section 17.2. The use of subject diaries is described in Section 10.5.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

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

1. The subject or legally authorized representative (in case of study participants <18 years of age) gave written informed consent to participate in the study.
2. Subject has hemophilia B.
3. Subject is defined as previously-treated patient (PTP):
   - Subject aged ≥ 6 years that has been previously treated with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 150 EDs.
   - Subject aged < 6 years that has been previously treated with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 50 EDs.
4. .Subject has no evidence of a history of FIX inhibitors.
5. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm^3, as confirmed by central laboratory at screening.
6. Subject is hepatitis C virus negative (HCV-) by antibody or PCR testing (if positive, antibody titer will be confirmed by PCR), as confirmed by central laboratory at screening; or HCV+ with chronic stable hepatitis.
7. The subject is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

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

1. Subject has known hypersensitivity or presence of any contraindication to RIXUBIS or its excipients including hamster protein.
2. Subject has evidence of an ongoing or recent thrombotic disease, fibrinolysis or disseminated intravascular coagulation (DIC).
3. 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.
4. 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.

5. 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.
6. Subject has severe chronic hepatic dysfunction [eg, ≥ 5 times upper limit of normal alanine aminotransferase (ALT), as confirmed by central laboratory at screening, or a documented INR > 1.5].
7. Subject has severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening.
8. Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia B.
9. Subject's platelet count is < 100,000/mL.
10. 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.
11. 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 antiretroviral chemotherapy.
12. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
13. Subject is a family member or employee of the investigator.

9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (ie, reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) are described in Section 10.6 and Section 20.2.

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

Note: If any subject develops FIX inhibitors during the study, they will be withdrawn from the study and treated as per SOC at the discretion of the Investigator (Note: RIXUBIS will not be used for ITI).

Note: Subject will also be withdrawn from the study if the subject needs an emergency surgery during the study.

All withdrawn or discontinued subjects need to complete the assessments to be performed at the termination visit as described in Section 20.2 and Section 20.3.

10. STUDY PROCEDURES

10.1 Informed Consent

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

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (eg, 251602) to be provided by the sponsor, 2- or 3-digit number study site number (eg, 02) to be provided by the sponsor, and 3 digit subject number (eg, 003) reflecting the order of providing informed consent. For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 251602-02003. All study documents (eg, CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (eg, collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome.

The overall study design is illustrated in Figure 1.

Details on the procedures to be performed at each study visit, including screening, can be found in Section 20.2 Schedule of Study Procedures and Assessments and Section 20.3 Clinical Laboratory Assessments.

10.4 Medications and Non-Drug Therapies

The physician is expected to follow standard clinical practice and all kinds of medications and/or non-drug therapies are allowed.

If any subject develops FIX inhibitors during the study, they will be withdrawn from the study and treated as per SOC at the discretion of the Investigator (Note: RIXUBIS will not be used for ITI).

10.5 Subject Diary

A paper subject diary will be provided to each subject at screening and at 1 month and 3 month visits to record the following information:

1. Infusion record of RIXUBIS (date, time of the infusion, number of units infused, number of vials utilized, lot number, and reason for infusion [bleeding episode, or prophylactic infusion])
2. Details of bleeding episodes (site, type, and severity of bleeding) and response to treatment as described in Section 11.1
3. All AEs will be recorded that do not fall within the provisions of Section 12.3.
4. Concomitant medications taken (including immunizations) and non-drug therapy
5. Drug accountability (number of unused vials of IP remaining in the subject's refrigerator will be recorded, prior to each study visit).

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in paper format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner. Untoward events recorded in the diary will be reported as AEs according to the investigator's discretion and clinical judgment.

The subject diary will serve as a source record and remain at the study site. Entries in the subject diary will be transferred into the appropriate collection device. Any entry in the collection device that does not correspond with an entry in the subject diary will be explained by the investigator in source documentation.

10.6 Subject Completion/Discontinuation

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

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

Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study completion/termination visit. If the completion/termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the completion/termination visit. If a subject terminates participation in the study and does not return for the completion/termination visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

The physician/investigator shall provide follow-up information on subjects who experienced serious adverse events until a diagnosis and final outcome are established or 30 days after the termination visit whichever is earlier. The sponsor will bear the cost of medical management of SAEs assessed as related to RIXUBIS therapy.

10.7 Procedures for Monitoring Subject Compliance

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

11. ASSESSMENT OF EFFICACY

11.1 Effectiveness of RIXUBIS as On-demand and Prophylaxis Treatment

In all cases, the treatment with RIXUBIS will be at the discretion of the investigator and will consist of either a prophylactic or on-demand treatment as per the RIXUBIS Product Label for India. The following information will be recorded by the subject, the subject's legal representative (for home treatment) or by authorized, qualified personnel at the participating site (for hospital-based treatment in case of a bleeding episode):

- Location of bleed, ie, joint, soft tissue, muscle, body cavity, intracranial, other
- Type of bleed, ie, spontaneous, injury, unknown
- Severity of bleed, ie, minor, moderate, major, life/limb threatening
- Date and time of onset of bleed
- Date and time of each infusion of RIXUBIS required to achieve adequate hemostasis
- Date and time of resolution of bleeding episode
- Type and number of analgesics required
- Overall effectiveness assessment for on-demand or prophylaxis treatment as described in Section 20.4.

If a bleed occurs following resolution of the bleed, it will be considered to be a "new" bleed and recorded accordingly.

Subjects will resume their prophylactic treatment regimen the next scheduled day after the last therapeutic infusion for the treatment of a bleeding episode.

Details pertaining to all home treatments for each bleed, including response to treatment, will be recorded by study subjects or the subject's legal representative in subject diaries provided by the study sponsor. At each study visit the investigator will review together with the subject the response to treatment and evaluate the hemostatic efficacy rating. Any inconsistency between the efficacy rating and the number of infusions required to treat a bleeding episode, or a response to treatment rated as "none" must be immediately clarified. If 2 or more responses to treatment are rated with "fair", the investigator may re-evaluate the dosing regimen, and the time from bleeding onset to start of treatment. In case more than one infusion was given to treat a bleeding episode, but the treatment was rated with "excellent", information should be provided about the severity of the bleeding episode and/or whether additional infusions were given to maintain hemostasis.

If infusions were given to maintain hemostasis after resolution of bleed, this should be recorded accordingly in the CRF. It may become necessary to re-discuss the rating with the subject to ensure that the Rating Scale is fully understood. In case of bleeding episodes requiring only one infusion but response to treatment rated with "fair" should also be evaluated.

Note: The Investigator must confirm all the efficacy ratings entered in the subject diary. If the Investigator identifies any inconsistency/error in the efficacy rating, Investigator will make their own assessment in conjunction with the subject (or the subject's legal representative) and enter it into the CRF. In cases where there are 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.

If, at any time during the course of the study, a subject's bleeding episode does not adequately respond to RIXUBIS therapy, he/she will be evaluated for the presence of inhibitory or total binding antibodies to FIX and clinically managed at the discretion of the investigator. In addition, AEs and the details of concomitant medication use coincident with the treatment of all acute bleeds will be recorded. Note that bleeding episodes are not to be reported as AEs (Section 12.1.2).

Any non-study FIX therapy or hemostatic product use administered for a bleeding event will be recorded on the appropriate section of the subject's diary and the CRF. The use of a FIX concentrate other than RIXUBIS will disqualify the subject from further participation in the study.

11.2 Determination of Incremental Recovery Over Time

FIX levels to determine IR will be assessed at visits as per Section 20.3.

Subjects will be infused with a dose of RIXUBIS. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 ml of saline solution. The procedures for blood sampling are described in Section 11.3.

Table 1.
Time Points of Determination of FIX activity

Assessment of recovery	Pre-infusion	0-30 minutes prior to infusion
	Infusion of RIXUBIS	
	Post-infusion	30 minutes ± 5 minutes

The sample for measurement of FIX activity will be obtained from an extremity different from that used for the infusion of IP.

11.3 Blood Sampling for Determination of Factor IX Level

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

For all clotting assays, citrated whole blood will be spun in **a refrigerated centrifuge (2 to 8°C)** at ≥ 2000 x gravity for approximately 20 minutes in capped tubes **within 2 hours of collection**. The plasma supernatant will be re-centrifuged at the same rate and duration to ensure removal of platelets and other particulate matter.

At least three aliquots of 0.6 mL of the centrifuged, citrated plasma will be pipetted into appropriate storage tubes, capped, labeled, and **stored in a freezer at ≤ -70°C, ideally within 15 minutes, but no later than 30 minutes after processing.**

All citrated plasma samples will be stored and shipped to the central laboratory at ≤ -70°C for testing. All samples will be maintained capped to the greatest extent possible. All citrated plasma samples will be assayed for FIX activity using the one-stage aPTT-based assay method.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

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

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.

12.1.1.1 Serious Adverse Event

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

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

- Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)
- As pertains to this study, further examples of medically important events include, but are not limited to:
  - Thromboembolism/DIC/Fibrinolysis
  - FIX inhibitor development (≥ 0.6 BU)
  - Nephrotic syndrome.

12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment (i.e., including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Once determined to meet the criteria for a SUSAR, a SAE should be submitted to regulatory agencies expeditiously.

12.1.1.3 Non-Serious Adverse Event

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

12.1.1.4 Unanticipated Adverse Device Effect

An **unanticipated adverse device effect** (UADE) is defined as any **serious** adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study protocol or product labeling, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

12.1.1.5 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). "Unexpected" also refers to the AEs that are mentioned in the IB and/or prescribing information as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation. The expectedness of AEs will be determined by the sponsor using the IB and/or prescribing information as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated form the pharmacological properties of a product.

12.1.1.6 Preexisting Diseases

Preexisting diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF.

12.1.2 Assessment of Adverse Events

For the purposes of this study, the following non-serious events experienced after the first IP exposure are collected under other study endpoints and thus are not reportable on the AE CRF, nor will they be included in the analysis of AEs:

1. Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be assessed as part of the efficacy assessments. However, the Investigator may decide that the event is an AE if the event also would have occurred in a normal patient under the same circumstances. If a bleeding episode was caused by an injury, the injury will be reported as an AE. Bleeding events will not be considered as AEs if they do not qualify as an SAE. All bleeding episodes must be entered in the bleeding event CRF.
2. Elective and planned surgeries when these surgeries relate to a preexisting disease that has not worsened during study participation will not be considered as (S)AEs.
3. Any pregnancy that occurs after maternal or paternal administration of medicinal product will be reported on a Pregnancy Report Form and followed-up at estimated date of delivery and 1 year post-delivery, if feasible. Any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.

4. Deviations from the protocol-specified dosage (including overdosing, underdosing, abuse and or misuse, withdrawal, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the dosing schedule defined in the package insert). Definition of under- and overdosing is done as per the judgment of the treating physician. Failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.
5. Preexisting diseases that are present before entry into the study are described in the medical history, and those that manifest with the same severity, frequency, or duration during the study, will not be recorded as AEs/SAEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF.

All other/Each AE from the first IP exposure until study completion or discontinuation date will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

1. Seriousness as defined in Section 12.1.1.1
2. Severity as defined in Section 12.1.2.1
3. Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (ie, the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

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

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

1. Mild
    - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
    - The AE resolves spontaneously or may require minimal therapeutic intervention.
2. Moderate
    - The AE produces limited impairment of function and may require therapeutic intervention.
    - The AE produces no sequela/sequelae.
3. Severe
    - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
    - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

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

1. Not related (both circumstances must be met)
    - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs

- Is not associated with the IP (ie, does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).

2. Unlikely related (either 1 or both circumstances are met)
   - Has little or no temporal relationship to the IP
   - A more likely alternative etiology exists
3. Possibly related (both circumstances must be met)
   - Follows a reasonable temporal relationship to the administration of IP
   - An alternative etiology is equally or less likely compared to the potential relationship to the IP
4. Probably related (both circumstances must be met)
   - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
     - Reappearance of a similar reaction upon re-administration (positive rechallenge)
     - Positive results in a drug sensitivity test (skin test, etc.)
     - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
   - Another etiology is unlikely or significantly less likely

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

12.1.2.3 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Section 20.2) and Section 12.1.2.

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

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the investigational product, must be reported immediately (within 24 hours of the study center's first knowledge of the event) by completing the paper SAE Report

Form and transmitting it to the Sponsor (for contacts and instructions refer to the SAE Report form). The site must enter all SAE data as reported on the paper SAE Report Form on the applicable eCRF pages.

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

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

12.1.3 Medical Device Safety reporting

The IP kit contains the BaxJect device. All Serious Injuries (SI) and Unexpected Adverse Device Events (UADE) must be reported to the sponsor as an SAE in the same process as described above.

Serious injury is defined as:

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

12.2 Urgent Safety Measures

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

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

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible EC(s) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

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

12.4 Non-Medical Complaints

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

1. A failure of a product to exhibit its expected pharmacological activity and/or design function, eg reconstitution difficulty
2. Missing components
3. Damage to the product or unit carton

4. A mislabeled product (eg, potential counterfeiting/tampering)
5. A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

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

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

Medical history will include the collection of hemophilia history, bleeding episode history, and history of any hemophilia product usage for 6 months prior to screening. Relevant medical and surgical history and all medications taken 3 months prior to screening will also be collected.

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

12.6 Physical Examinations

At screening and subsequent study visits (as described in Section 20.2), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.6), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.7 Clinical Laboratory Parameters

12.7.1 Hematology and Clinical Chemistry

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

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

Blood will be obtained for assessment of hematology and clinical chemistry parameters as per Section 20.3. Hematology and clinical chemistry assessments will be performed on EDTA-anticoagulated whole blood and serum, respectively, at the central laboratory. In addition, assessments may be performed whenever clinically indicated.

12.7.2 Urinalysis

A urine sample will be obtained for assessment of protein content using a dipstick at visits as per Section 20.3. A urinalysis should also be performed if inhibitors are detected or whenever clinically indicated. Urinalysis will be performed at the central laboratory.

12.7.3 Immunology Tests

The following immunology tests will be performed:

- Total binding and inhibitory antibodies to FIX
- Antibodies to CHO proteins and rFurin

The schedule for the immunology tests is shown in Section 20.3. All immunology tests should be performed after a wash-out period of at least 72 h after the last dose of RIXUBIS and subjects should not be actively bleeding.

12.7.3.1 Testing for Inhibitory and Total Binding Antibodies to Factor IX

Testing for inhibitory anti-FIX antibodies will be performed on citrate-anti-coagulated plasma, prepared as described in Section 11.3. All plasma samples will be tested using an assay based on the Nijmegen modification of the Bethesda method [5,6,7] in the central laboratory. Local laboratory results are to be used by the investigator for the clinical management of the subject, if applicable. When the results of the FIX inhibitor assay in the central laboratory and the local hemostasis laboratory are discordant, the result from the central laboratory will take precedence and be used in all analyses.

Inhibitory anti-FIX antibodies will be further characterized as described in Section 12.7.3.2.

Testing for total binding anti-FIX antibodies will be performed on citrate-anti-coagulated plasma, prepared as described in Section 11.3, using an enzyme-linked immunosorbent assay (ELISA) employing polyclonal anti-human immunoglobulins (IgG, IgM, IgA, IgD) antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results. Samples that show a binding antibody titer ≥ 1:80 will be further analyzed as described in Section 12.7.3.2.

12.7.3.2 Development of Inhibitory or Total Binding Antibodies to FIX

If an inhibitory antibody with a titer ≥ 0.6 BU is detected, the inhibitor will be confirmed in the central laboratory within 2 weeks of study site notification of the original central laboratory result. Subjects who develop an inhibitor that changes from a low to a high titer inhibitor or from a high titer to a low titer upon a second evaluation should return to the study site for a third inhibitor test with a suggested minimum wash-out phase of 72 hours within 2 weeks of the second inhibitor assessment. Once a low (0.6 to 5 BU) or a high titer (> 5 BU) inhibitor is confirmed, the subject will be withdrawn from the study. Any inhibitor confirmed by the central laboratory must be recorded as an SAE (Section 12.1.1.1).

If total binding antibodies with a positive titer of 1:80 or more are detected, an additional blood sample will be drawn at the next study site visit, but within 2 ± 1 weeks to confirm the result. Subjects developing total binding antibodies with a titer ≥ 1:80 will continue in the study.

To verify the FIX inhibitor, additional testing might be initiated, such as anti-phospholipid antibodies and lupus anticoagulans and/or FIX antibody testing using a different methodology, if necessary.

All tests will be performed at a defined central laboratory.

12.7.3.3 Antibodies to Chinese Hamster Ovary proteins and rFurin

Citrated plasma will be assayed for the presence of antibodies to CHO protein and rFurin:

- **Antibodies to CHO Protein:** For this assay, CHO protein derived from cultures of untransfected cells will be used. Testing for binding anti-CHO protein antibodies will be done on citrate-anti-coagulated plasma (prepared as described in Section 11.3) using an ELISA employing polyclonal anti-human IgG antibodies.

Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

- **Antibodies to rFurin:** An ELISA for detection of antibodies to human rFurin will be conducted. Testing for binding anti-human rFurin protein antibodies will be done on citrate-anti-coagulated plasma (prepared as described in Section 11.3) using an ELISA employing polyclonal anti-human IgG antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.7.4 Development of severe allergic reactions and anaphylaxis

In very rare cases, subjects **with hemophilia B** may develop severe allergic reactions following exposure to a FIX concentrate manifesting as pruritus, urticaria, erythema, angioedema, and/or dyspnea, which may progress to a life-threatening anaphylaxis with bronchospasm and hypotension. These reactions may occur concurrently or prior to the development of a FIX inhibitor.

Blood samples will be drawn for the following tests to be performed at the central laboratory:

Within 1 hour, if feasible, and 24 h following the severe allergic reaction/ anaphylaxis:

- hs-CRP
- Immune complexes: Two assays will be used to determine the presence of circulating immune complexes (CIC):

  CIC-C1q: The MicroVue CIC-C1q assay uses highly pure, functional human C1q coated in the solid phase to capture immune complexes. In the first stage, CIC in the diluted patient samples and heat-aggregated gamma globulin in the controls and standards are dispensed into the C1q coated assay wells. After incubation, unbound material is removed in a washing step and a ready-to-use conjugate (goat anti-human Ig-HRP) is added. After a second incubation, unbound conjugate is washed away. After addition of a substrate and a short incubation interval, the quantity of CIC in the sample (µg Eq/ml) can be determined by comparison to a standard curve.

  CIC-C3: The MicroVue CIC-Raji Cell Replacement ELISA assay uses a proprietary monoclonal antibody to a common neoantigen expressed on C3d, iC3b, and C3d,g to capture C3d containing immune complexes in human serum or plasma. In the first stage, CIC in the diluted patient samples and HAGG in the controls and standards are dispensed into the coated assay wells.

After incubation, unbound material is removed in a washing step and a ready-to-use conjugate is added. After a 30-minute incubation unbound conjugate is washed away. After addition of a substrate and a short incubation interval, the quantity of CIC in the sample (µg Eq/mL) can be determined by comparison to a standard curve.

- IgE: The presence of IgE will be determined by using the ImmunoCAP, a FIX-specific IgE blood test (Phadia®). The basis of the ImmunoCAP® technology is a cellulose polymer in a plastic capsule providing a large surface for protein binding. rFIX is covalently coupled to the solid phase using cyan-bromide activation of the cellulose polymer. Testing for binding IgE anti-human FIX antibodies will be done with 0.5 mL serum. Antibody-containing samples will be identified and titrated in a screening assay followed by a confirmatory assay to exclude false positive results.

After a minimum wash-out period of 72 hours following exposure to RIXUBIS:

- Inhibitory and total binding anti-FIX antibodies.
- Other assays may be considered.

Back-up blood samples drawn prior to the most recent infusion of RIXUBIS (see Section 12.7.6) will also be tested for the assays mentioned above to serve as baseline.

12.7.5 Other Laboratory Tests

FIX antigen will be measured using a commercially available ELISA kit at visits as per Section 20.3. The samples will be prepared as described in Section 11.3.

12.7.5.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each abnormal laboratory value will be recorded on the CRF. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes an new AE (see definition in Section 12.1, and record the sign, symptom, or medical diagnosis on the AE CRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.6), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, ie because it is due to a preexisting disease, due to a lab error, or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

Any seroconversion result for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V) shall be re-tested.

12.7.6 Backup Samples and Biobanking

Backup samples taken and stored short-term may be used for example for re-testing, follow-up of an AE(s) or other test results, and/or assay development. After study testing is completed, the remaining samples may be stored in a coded form for no more than 2 years after the final study report has been completed and then the samples will subsequently be destroyed.

For subjects < 6 years of age, back-up samples are optional; for subjects < 12 years of age, back-up samples for serum are optional.

12.8 Vital Signs

Not Applicable, vital signs will not be evaluated in this study.

Vital signs will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (in or cm) and weight (lb or kg) will also be collected.

Vital signs will be measured at visits as per Section 20.3. Blood pressure will be measured when subjects are in the supine position.

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

12.9 Special Treatment Consideration

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

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

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

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

Sometimes, these reactions can be life-threatening. Therefore, all patients should be closely monitored for signs or symptoms that could result from such reactions, educated on the signs or symptoms of these types of reactions, and instructed to contact the study site immediately if any of the symptoms are experienced following an injection.

If a patient experiences an acute allergic/hypersensitivity reaction after an injection of IP, he should be managed appropriately and given instruction to receive relevant supportive care. Additionally, for an event judged by the Investigator to be a potential systemic allergic/hypersensitivity reaction, blood samples will be collected for anti-FIX, anti Furin antibodies.

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

13. STATISTICS

Data handling will be conducted by the contract research organization. The data will be inspected for inconsistencies by performing validation checks.

Statistical analysis for this study will be descriptive in nature. All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the statistical analysis plan (SAP) prepared by the contract research organization and approved by the sponsor before database lock.

13.1 Sample Size and Power Calculations

Based on data from the WFH from 1998-2006, the mean prevalence of hemophilia B in India was 0.19 per 100,000 male. In the WFH Report on the Annual Global Survey 2014, 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 in switching patient from current therapy, an estimated study size of 25 subjects will be recruited.

13.2 Analysis Sets

13.2.1 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. This dataset will be used for the efficacy analyses.

13.2.2 Safety Analysis Set (SAS)

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

13.3 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 a study period will be included in the analyses up to the time of withdrawal.

13.4 Methods of Analysis

13.4.1 Primary Outcome Measure

The number of possibly or probably related SAEs (including FIX inhibitors) as well as the number of subjects with possibly or probably related SAEs (including FIX inhibitors) that occurred during or after first RIXUBIS infusion will be summarized.

13.4.2 Secondary Outcome Measures

13.4.2.1 Safety

The number of possibly or probably related adverse events as well as the number of subjects with possibly or probably related adverse events that occurred during or after first RIXUBIS infusion will be summarized.

Shift tables will be presented for the results of clinical laboratory data.

Subjects developing binding IgG or IgM antibodies to FIX or antibodies to CHO proteins or rFurin will be summarized.

13.4.2.2 Efficacy

Summary statistics will be provided for the rate of success of RIXUBIS for treatment of bleeding episodes as well as for the annualized bleeding rate (ABR) with prophylactic use of RIXUBIS. These tables will be also presented by bleeding site, cause and severity.

13.5 Planned Interim Analysis of the Study

No interim analyses are planned for this study.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

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

15.1.1 Final Clinical Study Report

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

15.2 Training

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

15.3 Monitoring

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

15.4 Safety Monitoring

The safety of the subjects in this study shall be monitored on the continuing basis as per the study Medical Monitoring Plan.

RIXUBIS is already approved in India and many other regions including US and EU. No actions relating to safety have been taken by the marketing authorization holder, sponsor, regulatory authorities, and data monitoring committees, or ethics committees thus far on RIXUBIS.

15.5 Auditing

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

15.6 Non-Compliance with the Protocol

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

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

15.7 Laboratory and Reader Standardization

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

16. ETHICS

16.1 Subject Privacy

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

16.2 Ethics Committee and Regulatory Authorities

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

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

16.3 Informed Consent

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

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

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

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the CTA.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.8), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

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

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

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

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

17.3 Document and Data Retention

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

18. FINANCING AND INSURANCE

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

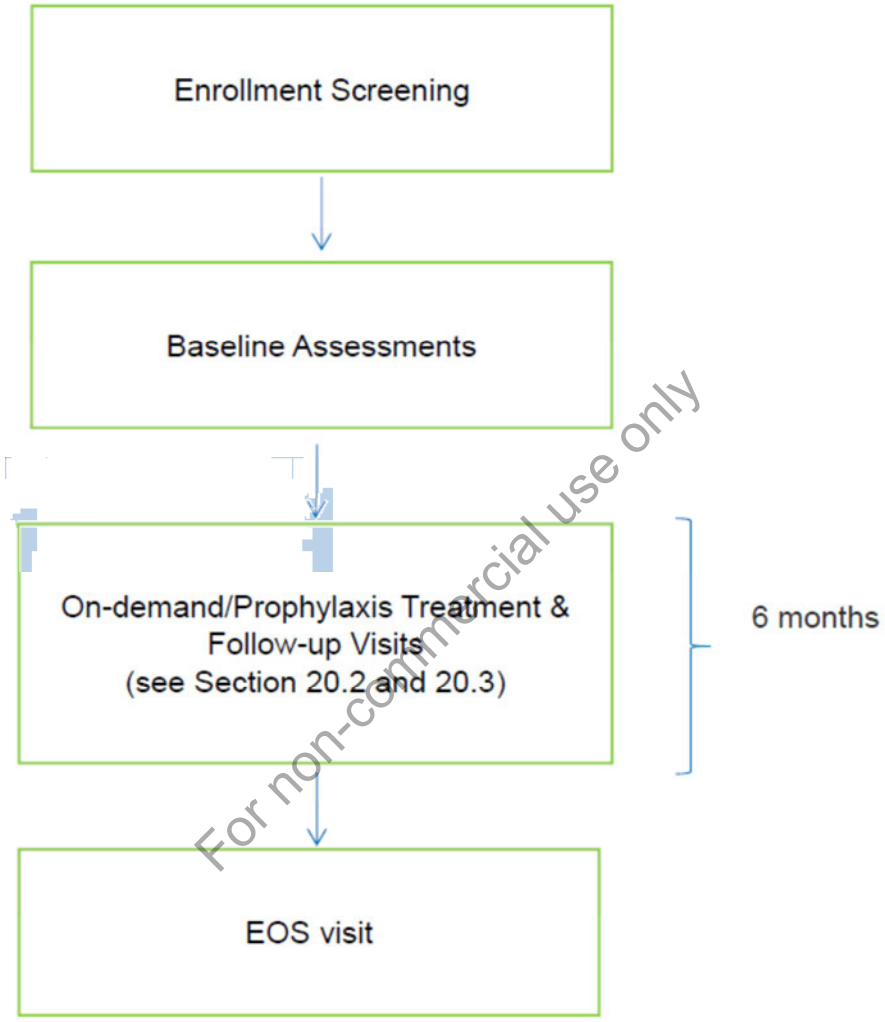
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 2.
Visit Schedule for Baxalta Clinical Study 251602



20.2 Schedule of Study Procedures and Assessments

Table 2.
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 month ± 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
Laboratory assessments[f]	See Table 3						
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 Use	X	X	X	X	X	X	X
RIXUBIS Dispense[h]		X	X	X	X		
End of Study Form						X	X

Continued on next page

Continued

[a] Defined 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. At all assessments, subjects must not 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.

20.3 Clinical Laboratory Assessments

Table 3.
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 month ± 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] Defined 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 (ie, 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.

20.4 Assessment of Effectiveness

Total number (%) of treated bleeds and their corresponding hemostatic effectiveness ratings using an "excellent-to-none" 4-point Likert scale by the subjects/care-giver (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.

Table 4.
Overall Effectiveness Assessment for On-Demand Treatment

Excellent	Full relief of pain and cessation of objective signs of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) within approximately 6 hours to 12 hours and after 1 or 2 infusions. No additional infusion is required for the control of bleeding. Any additional infusion for treatment of bleeding will preclude this rating. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding within approximately 6 hours to 24 hours requiring more than 2 infusions for complete resolution. Administration of further infusions to maintain hemostasis would not affect this scoring.
Moderate	Probable and/or slight relief of pain and slight improvement in signs of bleeding within approximately 6 hours to 24 hours. Requires multiple infusions for complete resolution.
None[i]	No improvement of signs or symptoms or conditions worsen.

Table 5.
Overall Effectiveness Assessment for Prophylaxis Therapy

Excellent	Definitely low bleeding rate with improvement in daily activities and quality of life. Very satisfied with the treatment and worth being continued
Good	Relatively low bleeding rate with some improvement in daily activities and quality of life. Satisfied with the treatment and worth being continued
Moderate	Relative increase in breakthrough bleeding episodes with only partial benefit in terms of activity level and quality of life. Partially satisfied with the treatment. Not sure if it is worth continuing treatment
None[i]	Frequent breakthrough bleeding episodes interfering with activity level and quality of life. Not satisfied with the treatment.

[i] If checked, the investigator should determine whether it is considered as "lack of effect" and, if yes, it should be considered as AE

21. REFERENCES

1. Puetz J, Soucie JM, Kempton CL, Monahan PE, Investigators HTCN. Prevalent inhibitors in haemophilia B subjects enrolled in the Universal Data Collection database. *Haemophilia*. 2014;20(1):25-31.

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3. 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.

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5. Verbruggen B, Novakova I, Wessels H, Boezeman J, van den Berg M, Mauser-Bunschoten E. The Nijmegen Modification of the bethesda assay for factor VIII: C inhibitors: improved specificity and reliability. *Thromb Haemost*. 1995;73(2):247-251.

6. Hay CRM, Brown S, Collins PW, Keeling DM, Liesner R. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Orgranisation. *Br J Haematol*. 2006;133(6):591-605.

7. Ewing NP, Kasper CK. In vitro detection of mild inhibitors to factor VIII in hemophilia. *Am J Clin Pathol*. 1982;77(6):749-752.

22. SUMMARY OF CHANGES

Protocol 251602: Amendment 2 2017 SEP 27

Replaces: Amendment 1: 2016 SEPT 15

In this section, changes from the previous version of the Protocol Amendment 1, dated 2016 SEPT 15, are described and their rationale is given.

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

2. Throughout the document
   Description of Change: The earlier version (Protocol Amendment 1, dated 2016 SEPT 15) used the Post Marketing Surveillance (PMS) study protocol template. An Interventional study protocol template has been used for this amendment. The 2 protocol templates (PMS study protocol template and Interventional study protocol template) are very different and almost all sections have been changed to reflect that.
   Purpose for Change: Since we are providing IP free of cost and since we are doing a mandatory inhibitor testing as per the recommendation from the Indian Health Authority, this study is now an Interventional study.

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: RIXUBIS Coagulation Factor IX (Recombinant)

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

PROTOCOL IDENTIFIER: 251602

CLINICAL TRIAL PHASE IV

AMENDMENT 2: 2017 SEP 27

Replaces: Amendment 1: 2016 SEP 15

ALL VERSIONS:
Amendment 2: SEP 27
Amendment 1: 2016 SEP 15
Original: 2016 APR 25

OTHER IDs:
NCT Number: pending
EudraCT Number: not applicable
IND NUMBER: not applicable

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

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: RIXUBIS Coagulation Factor IX (Recombinant)

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

PROTOCOL IDENTIFIER: 251602

CLINICAL TRIAL PHASE IV

AMENDMENT 2: 2017 SEP 27

Replaces: Amendment 1: 2016 SEP 15

ALL VERSIONS:
Amendment 2: 2017 SEP 27
Amendment 1: 2016 SEP 15
Original: 2016 APR 25

OTHER IDs:
NCT Number: pending
EudraCT Number: not applicable
IND NUMBER: not applicable

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

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

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

OBSERVATIONAL STUDY PROTOCOL

RIXUBIS Coagulation Factor IX (Recombinant)

(NONACOG GAMMA)

A Post Marketing Surveillance (PMS) study of RIXUBIS in India

Short Title: RIXUBIS PMS India

(RIXUBIS PMS)

PROTOCOL NUMBER: 251602

AMENDMENT 1: 2016 SEP 15

REPLACES ORIGINAL: 2016 APR 25

Study Sponsor(s): **Baxalta Innovations GmbH**
Industriestrasse 67
A-1221 Vienna, AUSTRIA

1. STUDY PERSONNEL

Authorized Representative (Signatory)	Sponsor's Medical Expert
Baxalta Innovations GmbH	[redacted] MD
Industriestrasse 67	[redacted] Global Clinical Development
A-1221 Vienna, AUSTRIA	Baxalta Innovations GmbH

1.1 Study Organization

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

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the Ethics Committees. For information on the definition and assessment of adverse events (AEs), refer to Section 12.5.

ALL SAEs ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE MAH WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT

See SAER form for contact information.

Further details are also available in the study team roster.

NON-SERIOUS ADVERSE EVENT REPORTING

Any non-serious adverse events (AEs), all therapies/procedures to treat the AEs, and the outcome of the AEs are to be reported to the MAH on the appropriate case report forms (CRFs) within 5 business days.

ADVERSE EVENT DEFINITIONS AND ASSESSMENT

For information on the definitions and assessment of these events refer to: definitions of AE in Section 12.1.1, SAE in Section 12.1.2 and assessment of AEs in Section 12.5.

3. SYNOPSIS

Observational Study Number	**251602**
Study Title	A Post Marketing Surveillance (PMS) study of RIXUBIS in India
Dates of Study	Enrollment will start within 3 months after commercial RIXUBIS is available for general use (expected to take place approximately on 31 JAN 2017). Patients will be enrolled for 2.5 years and followed up for 6 months. The expected study completion date is approximately 30 JAN 2020.
Objectives	*Primary objective* To characterize the safety of RIXUBIS when used under standard clinical practice in India. *Secondary objectives* To describe hemostatic effectiveness in subjects receiving RIXUBIS under standard clinical practice in India.
Active Ingredient(s)	Recombinant Factor IX (FIX)
Medicinal Product	Recombinant Factor IX (RIXUBIS)
Study Design	Multi-center, prospective observational non-interventional post-marketing study with no mandated treatments (refer to RIXUBIS PI), visits or assessments.
Treatment(s)	All subjects enrolled will be treated with RIXUBIS according to a regimen determined by the study site treating physician/investigator (i.e., on-demand treatment, prophylaxis treatment, and perioperative treatment).
Duration of Participation	Duration of study will be 36 months.

Subjects	The target enrollment is up to 25 subjects. Patients with congenital hemophilia B (FIX level ≤5%) who have been prescribed RIXUBIS according to the investigator's judgment shall be included as subjects if 1. The patient or legally authorized representative or family member (in case of study participants <18 years of age) gave written informed consent to participate in the study 2. The patient is indicated for treatment according to the RIXUBIS Indian product leaflet. According to the product label, the following patients should not be treated with RIXUBIS and therefore should be excluded from participation in this study if there is: 1. Known hypersensitivity or presence of any contraindication to RIXUBIS or its excipients including hamster protein.
Statistical Analysis:	All analyses will be descriptive and include arithmetic means, medians, standard deviations, minimum, maximum, 25th and 75th percentiles, frequency counts, proportions, and 95% confidence intervals of select point estimates.

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5. ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event (or Adverse Experience)
BU	Bethesda Units
CHO	Chinese Hamster Ovary
CRF	Case Report Form
DCGI	Drug Controller General of India
ED	Exposure Day
EFAS	Effectiveness full analysis set
EU	European Union
FIX	coagulation factor IX
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HTC	Hemophilia Treatment Center
ICF	informed consent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITI	Immune tolerance induction
IU	International Unit
Kg	Kilogram
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
NHR	India National hemophilia registry
SAE	Serious Adverse Event (or Serious Adverse Experience)
SAS	Safety analysis set
SIC	Subject identification code
WFH	World Federation of Hemophilia

6. INTRODUCTION

Hemophilia B is an X chromosome-linked recessive congenital disorder of blood coagulation due to decreased levels or complete lack of factor IX and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma.

Hemophilia B affects 1-2 infants per 50,000 male newborns. In patients with hemophilia B, susceptibility to uncontrolled bleeding is influenced by disease severity defined by the baseline plasma factor levels of >5% to <40% (mild), 1% to 5% (moderate), or <1% (severe). Of the patients with hemophilia B, approximately 26% reported to have mild, 38% had moderate and 36% had severe disease.[1]

According to the World Federation of Hemophilia (WFH) Report on the Annual Global Survey 2014, there were a total of 14,450 cases of hemophilia and 2,281 confirmed cases of hemophilia B in India in 2014.[2] The number of patients with hemophilia B in India who developed inhibitors was not available. Based on data from the WFH from 1998-2006, the mean prevalence of hemophilia B in India was 0.19 per 100,000 males.[3] The India National hemophilia registry (NHR) reports showed 50% 0f diagnosed hemophilia B patients are on factor IX treatment.

The age distribution of Hemophilia B in India is as follows: 3% between 0-4 years, 14% between 5-13 years, 13% between 14-18 years, 34% between 19-44 years and 7% 45+ years; age was unknown for 29% of patients with hemophilia B.[2]

The total IU of Factor IX in 2014 reported to the WFH was 1,226,400 IU, of which 100% was plasma-derived and 0% was recombinant Factor IX. In 2014, the per capita use of factor IX in India was 0.001 IU per capita. The per capita Factor IX use was consistent from the use reported from 1998-2006 (mean 0.001 IU per capita).[4] The average Factor IX use per patient with hemophilia B from 1998 to 2006 was 203 IU in India.[4] Replacement therapy increases the plasma level of factor IX, providing a temporary correction of the factor deficiency and the bleeding tendency.

One of the most serious complications of replacement therapy is the development of inhibitory antibodies against the exogenously applied coagulation factor in as many as 20-30% of patients with severe hemophilia A, and in 1-5% of patients with severe hemophilia B. The risk for inhibitor development to FIX depends on a number of factors relating to the characteristics of the patient, including: the causative FIX gene mutations, family history, ethnicity, intensity of treatment, and the early implementation of prophylactic treatment.

A substantial proportion of patients with FIX inhibitors have high responding, high titer inhibitors [>5 Bethesda units (BU)]. Inhibitor development in hemophilia B is associated with the development of anaphylactic reactions. Immune tolerance induction (ITI) is frequently less successful in these patients and subjects may develop a nephrotic syndrome as a result of ITI.

RIXUBIS (recombinant coagulation factor IX) is a single-chain purified glycoprotein that has 415 amino acids. It is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell line. RIXUBIS is not derived from human blood or plasma products, and its manufacturing process does not include animal or human proteins. RIXUBIS contains no preservatives. Recombinant coagulation factor IX is a single chain glycoprotein that is a member of the serine protease family of vitamin K-dependent coagulation factors.

Recombinant coagulation factor IX is a recombinant DNA-based protein therapeutic which has structural and functional characteristics comparable to endogenous factor IX. Factor IX is activated by factor VIIa/tissue factor complex in the extrinsic pathway and by factor XIa in the intrinsic coagulation pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. This results ultimately in the conversion of prothrombin to thrombin. Thrombin then converts fibrinogen into fibrin, and a clot can be formed.

6.1 Study Rationale

The results derived from the RIXUBIS clinical development program suggest that RIXUBIS is efficacious, has an acceptable safety profile, and well-tolerated in adults and pediatric subjects with severe to moderately severe hemophilia B in a variety of clinical settings.

This study will collect data on RIXUBIS administered to patients with hemophilia B in standard clinical practice and as per product leaflet.

The purpose of this study is to characterize the safety and describe the effectiveness of RIXUBIS in routine clinical practice

6.2 Clinical Efficacy

RIXUBIS is indicated in adults and children with hemophilia B for the control and prevention of bleeding episodes, perioperative management and routine prophylaxis RIXUBIS is licensed in 14 countries and the European Union; it has an acceptable safety profile and well-tolerated in the treatment of moderately severe to severe hemophilia B. The efficacy and safety of RIXUBIS was evaluated in 3 clinical studies: a pivotal trial, a pediatric trial, and a surgery trial. An additional continuation study is in progress. These studies involved overall 105 previously treated patients with severe to moderately severe hemophilia B. In all bleeds experienced, 85% were treated with 1-2 infusions and 96% rated haemostatic efficacy as excellent or good.

6.3 Safety

There is an identified risk of hypersensitivity reactions [including reactions/antibodies to Chinese Hamster Ovary (CHO) protein] to RIXUBIS. Potential risks include inhibitor formation, lack of effect, thromboembolic events and nephrotic syndrome following attempted immune tolerance induction in haemophila B patients with FIX inhibitors and a history of allergic reactions. RIXUBIS is not indicated for induction of immune tolerance in patients with Hemophilia B and contraindicated in known hypersensitivity to RIXUBIS or its excipients including CHO protein, disseminated intravascular coagulation (DIC) and signs of fibrinolysis. RIXUBIS treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia.

The integrated safety analysis indicated a low (<1%) incidence of adverse drug reactions (ADRs). A total of 337 AEs were reported in 80/99 (80.8%) subjects treated with at least 1 infusion of RIXUBIS. Most of the AEs were non-serious (327/337) and were not related (331/337) to the administration of RIXUBIS. There were no deaths and no subjects developed inhibitory antibodies to FIX and CHO proteins. There were no thrombotic events or severe allergic reactions.

No actions relating to safety have been taken by the marketing authorisation holder, sponsor, regulatory authorities, and data monitoring committees, or ethics committees thus far on RIXUBIS.

7. OBJECTIVES

7.1 Primary objective

To characterize the safety of RIXUBIS when used under standard clinical practice in hemophilia B patients in India. Specifically, data will be collected on all serious and non-serious adverse events, regardless of causality or expectedness, occurring coincident with use of RIXUBIS will be collected.

7.2 Secondary objective

To describe hemostatic effectiveness in subjects receiving RIXUBIS under standard clinical practice in hemophilia B patients in India.

8. STUDY POPULATION

8.1 Subject Selection Criteria

All patients with hemophilia B who are eligible to receive RIXUBIS in standard clinical practice.

8.2 Inclusion Criteria

Patients with hemophilia B (FIX level ≤5%) who have been prescribed RIXUBIS according to the investigator's judgment shall be included as subjects if:

1. The patient or legally authorized representative or family member (in case of study participants <18 years of age) gave written informed consent to participate in the study and
2. The patient is indicated for treatment according to the RIXUBIS India product label.

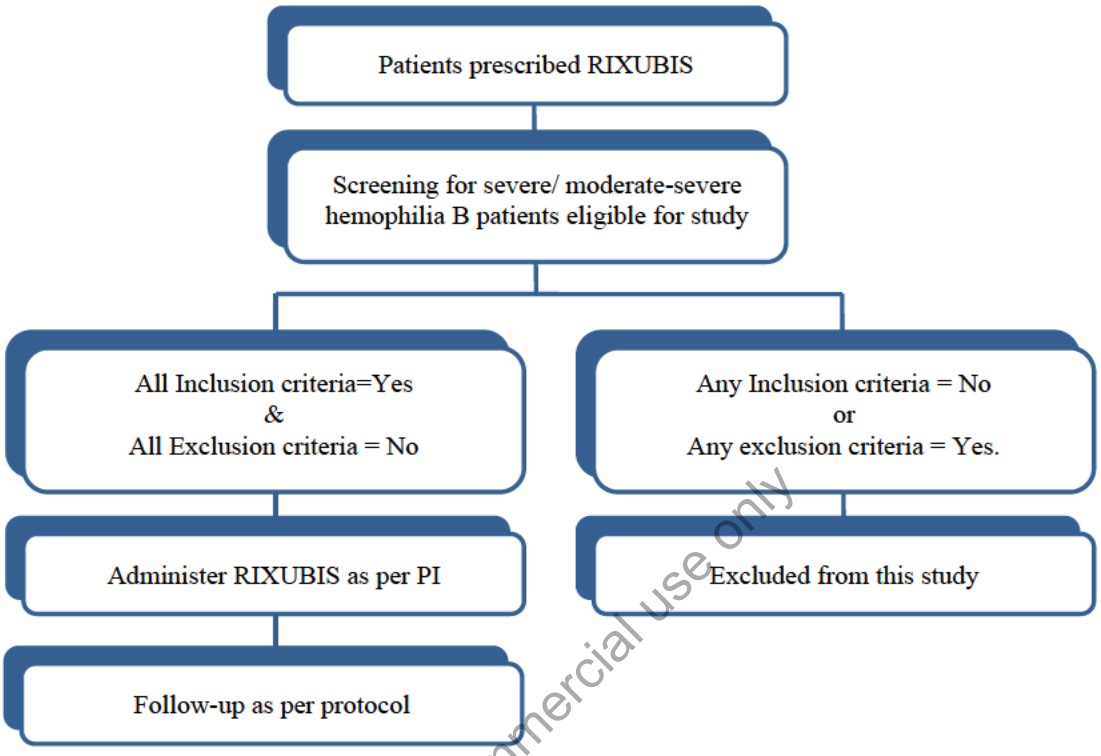
8.3 Exclusion Criteria

According to the product label, the following patients should not be treated with RIXUBIS and therefore should be excluded from participation in this study if there is:

1. Known hypersensitivity or presence of any contraindication to RIXUBIS or its excipients including hamster protein

9. STUDY DESIGN

Figure 1 Study Flow Chart



This is a prospective, uncontrolled, open- label, post-marketing, non-interventional safety surveillance study where the subjects have been prescribed RIXUBIS by their physicians as a choice of therapy. Based on data from the WFH from 1998-2006, the mean prevalence of hemophilia B in India was 0.19 per 100,000 male. In the WFH Report on the Annual Global Survey 2014, 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 in switching patient from current therapy, an estimated study size of 25 subjects will be recruited. The study follows a cohort design, and does not make binding stipulations on treatment schedule. Principally, the study aims to collect subject and treatment-related data of subjects on RIXUBIS therapy over a 36-month period.. Informed consent is required to be obtained prior to study enrollment. Eligible patients will be enrolled sequentially to avoid selection bias. Data for the assessment of safety and efficacy will be collected during subsequent routinely scheduled and unscheduled visits to the physicians' office which may occur during routine care.

All study subjects will be included in the assessments of safety and hemostatic effectiveness. The RIXUBIS regimen for this study will be chosen by the attending physician.

9.1 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study that are necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

For additional information on study documentation and CRFs, see Section 20.3

10. STUDY DURATION

The study will start within 3 months after commercial RIXUBIS is available for general use (expected to take place approximately on 31 JAN 2017). The subject is considered enrolled in the study once the informed consent is signed and dated. All data before enrollment (especially with a RIXUBIS treatment) will be collected in the Medical History. The follow-up period for each enrolled patient will be up to 6 months from first Physician visit after enrolment while on treatment. This shall be documented in at least 3 data collection points (Baseline, 1 month and 6 months). This period of follow-up is deemed adequate as most patients on prophylaxis will receive RIXUBIS twice weekly equaling 52 doses during the follow-up period. Additionally, for the control and prevention of bleeding episodes, patient could receive RIXUBIS for up to 10 days depending on the type of bleeding episode. Given our knowledge of the pharmacokinetics and safety profile of RIXUBIS, we believe hemostatic effectiveness can be assessed and any safety issues identified during the 6-month follow-up period. The study is expected to last until approximately 30 JAN 2020.

11. STUDY PROCEDURES

The physician is expected to follow standard clinical practice. The study aims to characterize the safety and describe haemostatic effectiveness of RIXUBIS when used under standard clinical practice of treating hemophilia B patients in India. It does not stipulate specific clinical or laboratory testing requirements beyond those done in routine clinical care, and those necessary to establish eligibility and safety. However, certain data will be captured, if available, during the course of the study

11.1 Initiation & Baseline Visit

- **Subject baseline data**
  - Date of visit
  - Date of signed consent
  - Year of birth
  - Age
  - Gender
  - Vital Signs
  - Baseline FIX levels (most recent prior to study enrollment)
  - Inhibitor titer/Inhibitor screening test
  - History of thromboembolism
  - Family history of inhibitors
  - Number of bleeding episodes by severity within the last 12 months.
  - Other pertinent medical history
  - Concomitant medications
- **History of inhibitor development**
  - Date(s) of inhibitor detection
  - Total FIX EDs at time of inhibitor detection or, if exact number not available, one of the following ranges: 0, 1-4, 5-20, 21-50, 51-100, 101-150 or >150.
  - FIX product used at the time of inhibitor detection
  - FIX regimen used at the time of inhibitor detection
  - Maximum historical titer

- Local laboratory cut off value for positive inhibitor titer
- History of ITI therapy, if any, including FIX product and regimen used
- Date(s) of inhibitor disappearance
- Most recent FIX inhibitor test results.

- **FIX Treatment History**
  - FIX product used prior to RIXUBIS treatment initiation (maximal retrospective time- period of 12 months before enrollment)
  - Name of product, dosage and dosing interval
  - Regimen start and end date
  - Total EDs to FIX products at baseline visit or, where exact number not available, one of the following ranges should be selected: 0, 1-4, 5-20, 21-50, 51-100, 101-150 or >150.

11.2 Every Visit

- **Visit Information**
  - Visit date
  - Visit type (outpatient/office, in-hospital, phone, other)
  - Reason (scheduled, emergency, other)
- **Current/Prescribed RIXUBIS treatment**
  - Indication for RIXUBIS (reason(s) for all active prescriptions)
    - Routine prophylaxis
      - Dosage and dosing intervals
      - Regimen start/change date
    - Control of bleeding
      - Type of bleeding episode (minor, moderate, major)
      - Dosage and Duration
      - Number of infusions to treat a bleed
    - Perioperative management
  - Total EDs to RIXUBIS or, where exact number of EDs is not available, one of the following ranges should be selected: 0, 1-4, 5-20, 21-50, 51-100, 101-150 or >150.

- **Clinical & Other Data**
  - Vital signs
  - Bleed occurrence
    - Location
    - Etiology
    - Severity
    - Frequency
    - Number of infusions to treat a bleed
  - Number of bleeds/month/year/ABR score (if available)
  - Postoperative hematomas
    - Dimensions
  - RIXUBIS clotting assay (if performed under routine care)
  - Concomitant medications
  - Non-drug therapies
- **Assessment of Safety**
  - Inhibitor to RIXUBIS
    - Date(s) of inhibitor detection
    - Date(s) of inhibitor disappearance
    - FIX inhibitor titer(s)
  - Other serious and non-serious adverse events
    - Event
    - Onset Date
    - Stop Date
    - Severity
    - Outcome
    - Action Taken
    - Date of death (if applicable)
    - Cause of Death (if applicable)
    - Causality assessment by Investigator

- **Assessment of Haemostatic Effectiveness**
  - Physician rated effectiveness[i] ("none", "moderate", "good", or "excellent")
  - Subject rated effectiveness[i]
  - Number of infusions to treat a bleed (prophylaxis or on demand)

11.3 Last Visit

- **Visit information**
  - Visit date
  - Visit type (outpatient/office, in-hospital, phone, other)
  - Reason (scheduled, emergency, other)
  - Inhibitor titer/Inhibitor screening test
  - Assessment of Safety and Haemostatic Effectiveness
- **End of study reason**
  - Study end, lost to follow-up, death, participant withdrawal, physician decision (specify), other , (details in section 14)

11.3.1 Subject Inclusion

11.3.1.1 Informed Consent and Enrollment

Any patient who directly, or indirectly through a legally authorized representative, provides informed consent (i.e., signs and dates the informed consent form and assent form, if applicable) is considered enrolled in the study. The study site is responsible for maintaining an enrollment log that includes all subjects enrolled.

11.3.1.2 Subject Identification Code

The following series of numbers will comprise the subject identification code (SIC): protocol identifier, two digit study site number (e.g., 02) to be provided by the MAH, and four digit subject number (e.g., 0003) reflecting the order of enrollment at each site. For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 251602-020003. All study documents pertaining to the subject (e.g., CRFs, clinical documentation, etc.) will be identified with the SIC.

[i] Criteria for effectiveness assessment in Appendix, Section 23.2

11.4 Clinical Assessments

11.4.1 Medical History, Medications, and Non-Drug Therapies

Medical history, comorbidities and other pre-existing conditions will be reported as available in the patient medical record. Specific data to be obtained is outlined in section 11.1 Findings from any physical examinations pertinent to these data elements should be reported in the CRF.

Hemophilia history and treatment history will be captured, including start and end dates of past treatments where available.

All relevant medications taken and non-drug therapies received from enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

11.4.1.1 FIX inhibitor testing

Patients on RIXUBIS therapy should be screened for inhibitor development at the beginning and at end of study (the intermediate time points is at the discretion of the treating Physicians) and in accordance with the WFH Guidelines as follows [5]:

- Confirmation of the presence of an inhibitor and quantification of the titre is performed in the laboratory, preferably using the Nijmegen-modified Bethesda assay.
- For children, inhibitors should be screened once every five exposure days until 20 exposure days, every 10 exposure days between 21 and 50 exposure days, and at least two times a year until 150 exposure days.
- For adults with more than 150 exposure days, apart from a 6-12 monthly review, any failure to respond to adequate factor concentrate replacement therapy in a previously responsive patient is an indication to assess for an inhibitor.
- Inhibitor measurement should also be done in all patients who have been intensively treated for more than five days, within four weeks of the last infusion.
- Inhibitors should also be assessed prior to surgery or if recovery assays are not as expected, and when clinical response to treatment of bleeding is sub-optimal in the post-operative period.

The investigator's assessment of FIX inhibitor level will be recorded on the CRF.
The inhibitor assay methods and reference standard used will be reported in the CRF.
In the case a positive inhibitor titer is detected, a confirmatory test on a second, separately drawn sample should be performed. This second sample should be taken prior to any

change of treatment and shortly (within 1 month) after the previous positive test (a positive inhibitor titer is considered to be ≥ 0.6 BU). For each abnormal FIX inhibitor value, the investigator will determine whether the value is clinically significant or not. For clinically significant values, the investigator will enter as new SAEs (see definition in Section 12.1.2). If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e. because it is due to a preexisting disease, due to a lab error, or due to another issue that will be specified. Any abnormal value that persists should be followed at the discretion of the investigator.

Any other clinically significant lab abnormality identified through standard clinical practice that meets the criteria for an adverse event (Section 12.1.1) shall be reported.

11.4.1.2 Vital Signs

Vital signs will include height (cm) and weight (kg), if available, at baseline visit or whenever assessed under normal clinical care or clinically significant.

11.5 Treatment with RIXUBIS

The choice of therapeutic approach (prophylaxis vs. on-demand) as well as dose and dosing regimens will be prescribed at the discretion of the investigator. The dosage and number of infusions of RIXUBIS required to achieve adequate hemostasis for each new bleeding episode will be recorded as well as all the RIXUBIS lot numbers. Details pertaining to infusions administered in the context of a home treatment will be sourced from diaries supplied to subjects by the Sponsor. If the subject receives RIXUBIS while undergoing a surgical or invasive procedure, data related to RIXUBIS therapy, effectiveness and safety will be recorded.

If, at any time during the course of the study, a subject's bleed does not respond to therapy with RIXUBIS it is recommended to screen for the presence of an inhibitor (see Section 11.4.1.1). All subjects will be treated at the discretion of the treating physician/investigator until adequate hemostasis is achieved. Additionally, details of concomitant medication used in conjunction with the treatment of all acute bleeding events will be recorded.

11.5.1 Summary Description of RIXUBIS

RIXUBIS (rFIX) is an antihaemophilic factor indicated in adults and children with hemophilia B for:

- Treatment and prevention of bleeding episodes in patients with hemophilia B (congenital factor IX deficiency)

- Routine prophylaxis of bleeding episodes in patients with hemophilia B
- Perioperative management in patients with hemophilia B

RIXUBIS is not indicated for induction of immune tolerance in patients with Hemophilia B.

RIXUBIS (recombinant coagulation factor IX) is a single-chain purified glycoprotein that has 415 amino acids. It is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell line. RIXUBIS is not derived from human blood or plasma products, and its manufacturing process does not include animal or human proteins. RIXUBIS contains no preservatives. Recombinant coagulation factor IX is a single chain glycoprotein that is a member of the serine protease family of vitamin K-dependent coagulation factors.

Recombinant coagulation factor IX is a recombinant DNA-based protein therapeutic which has structural and functional characteristics comparable to endogenous factor IX. Factor IX is activated by factor VIIa/tissue factor complex in the extrinsic pathway and by factor XIa in the intrinsic coagulation pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. This results ultimately in the conversion of prothrombin to thrombin. Thrombin then converts fibrinogen into fibrin, and a clot can be formed.

11.5.1.1 Packaging and Labeling

Please refer to the product label.

11.5.1.2 Shelf-life and Storage

Please refer to the product label.

11.5.1.3 Reconstitution

Please refer to the product label.

11.5.1.4 Routes and Modes of Administration

Please refer to the product label.

11.5.1.5 Dosing Schedule and Requirements

For up to date dosing information, please refer to the product label.

12. ASSESSMENT OF SAFETY

12.1 Definitions of Safety Events

12.1.1 Adverse Event (AE)

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

12.1.2 Serious Adverse Event (SAE)

An SAE is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death).
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above.
    - As pertains to this study, examples of medically important events include, but are not limited to:
        - Thromboembolism/DIC/Fibrinolysis
        - FIX inhibitor development (≥ 0.6 BU)
        - Nephrotic syndrome.

12.1.3 Non-Serious Adverse Event

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

12.1.4 Unexpected Adverse Events

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

12.2 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequelae, which require (prolonged) therapeutic intervention.

12.3 Causality

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

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not related to the RIXUBIS (i.e., does not follow a reasonable temporal relationship to the administration of RIXUBIS or has a much more likely alternative etiology).
- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the RIXUBIS
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of RIXUBIS
  - An alternative etiology is equally or less likely compared to the potential relationship to the RIXUBIS
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of RIXUBIS, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive rechallenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the RIXUBIS as evidenced by measurement of the RIXUBIS concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

12.4 Disease/Study Specific AE Considerations

- Preexisting diseases that are present before entry into the study are described in the medical history, and those that manifest with the same severity, frequency, or duration during the study, will not be recorded as AEs/SAEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF
- Bleeding events will not be considered as AEs if they do not qualify as an SAE. Elective and planned surgeries when these surgeries relate to a preexisting disease (see also Section 12.1.2) that has not worsened during study participation will not be considered as (S)AEs
- Any pregnancy that occurs after maternal or paternal administration of medicinal product will be reported on a Pregnancy Report Form and followed-up at estimated date of delivery and 1 year post-delivery, if feasible. Any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.
- The sponsor will bear the cost of medical management of SAEs assessed as related to RIXUBIS therapy.
- Overdosing, underdosing, abuse and or misuse, withdrawal, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the dosing schedule defined in the package insert). Definition of under- and overdosing is done as per the judgment of the treating physician. Failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

12.5 Assessment of Adverse Events

Each AE, from enrollment until study completion/discontinuation date, will be described on the AE CRF (i.e., 1 AE per form) using the medical diagnosis (preferred), symptom, or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1.1 Each AE, will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.2
- Severity as defined in Section 12.2
- Causal relationship to RIXUBIS exposure as defined in Section 12.3

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal) and action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until the study completion/termination visit.

12.6 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (mild, moderate, or severe as defined in Section 12.2) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All medications taken and non-drug therapies received from enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs

12.7 Assessment of Laboratory Values

12.7.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each abnormal laboratory value is to be recorded on the CRF form. For each abnormal laboratory value, the investigator will determine whether the value is also considered an AE (see definition in Section 12.1.1). If yes, the sign, symptom, or medical diagnosis will be recorded on the AE CRF. If the abnormal value was not deemed an AE because it was due to a lab error, was due to a preexisting disease, was not clinically significant, was a symptom of a new/worsened condition already recorded as an AE, or was due to another issue that will be specified, the treating physician/investigator will record the justification on the CRF form. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

If a FIX inhibitor (Bethesda titer ≥ 0.6 BU) is detected in any subject during the course of the study, the subject may continue on the study at the same or higher dose per infusion at the discretion of the study site treating physician/investigator, pending the outcome of subsequent inhibitor testing as directed by the study site investigator. If a new inhibitor is detected (≥ 0.6 BU), it must be reported as an SAE, and the corresponding SAE page must be completed and returned within 24 hours to the Sponsor (see Section 2).

If a subject tests positive for a FIX inhibitor, a confirmatory test on a second, separately drawn sample should be performed. This second sample should be taken prior to any change of treatment and shortly (within 1 month) after the previous positive test.

For methods of assessment see Section 11.4

13. SUBJECT WITHDRAWAL

Any subject may withdraw from the study for any reason at any time. Additionally, the investigator has the possibility to withdraw any subject from the study at his discretion. The investigator should provide the sponsor with a written account of any reasons for early withdrawal.

14. STUDY COMPLETION

The end-of-study CRF will be completed at study termination. The primary reason for termination will be listed on the CRF. One of the following conditions should be met:

a. Subject completed study.

b. Subject experienced adverse drug reaction(s) from the study drug necessitating discontinuance of treatment.

c. Subject was withdrawn by the primary investigator at the site for non-study drug related reasons.

d. Unsatisfactory therapeutic response to study product (as determined by the investigator).

e. Subject or legally authorized representative voluntarily withdrew consent.

f. Subject was lost to follow- up.

g. Subject died.

h. Other reason for premature study termination.

Regardless of the reason for termination, all data available for the subject up to the time of termination should be recorded onto the appropriate CRF, prior to retrieval by the Sponsor. In the event of premature study termination resulting from an adverse event, clinical and/or laboratory investigations that are beyond the scope of the required study observations may be performed as part of the evaluation of the event at the discretion of the study site investigator.

The physician/investigator shall provide follow-up information on subjects who experienced serious adverse events until a diagnosis and final outcome are established or 30 days after the termination visit whichever is earlier. The sponsor will bear the cost of medical management of SAEs assessed as related to RIXUBIS therapy

15. STATISTICAL ANALYSIS

15.1 Data Analysis Plan

15.1.1 Datasets and Analysis Cohorts

Safety Analysis Set (SAS)

All subjects having received RIXUBIS at any time during the study will be included in the safety analysis set.

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. This dataset will be used for the hemostatic effectiveness assessment.

15.1.2 Methods of Analysis

All analyses will be descriptive and include specifically but not exclusively, arithmetic means, medians, standard deviations, minimum, maximum, 25th and 75th percentiles, frequency counts, proportions and 95% confidence intervals of select point estimates. Figures will be prepared to illustrate the patterns of data over time where appropriate. The number of subjects included in each analysis set will be reported. Analyses will be performed using available data, due to the non-interventional nature of the study, missing values are expected.

16. DATA MANAGEMENT

All AEs that occurred during or after first RIXUBIS infusion will be categorized according to the MedDRA dictionary and summarized by system organ class and preferred term. AEs will be cross-tabulated for relatedness, seriousness, and severity. AEs that occurred before first RIXUBIS infusion will be listed separately. Any subject will be allotted a unique identification number described in Section 11.3.1.2, reflecting the order in which enrollment took place at that site. The subject's unique identification number is required for data allocation and evaluation. All data collected during the study will be entered in an electronic database for statistical analysis. Plausibility checks will be done, and attempts will be made to resolve inconsistencies.

17. OBLIGATIONS OF THE SPONSOR AND THE INVESTIGATOR

This study will be conducted in accordance with this observational protocol, the Declaration of Helsinki, and national regulations applicable to post-authorization surveillance studies.

The Sponsor will select Investigators on the basis of their expertise in the treatment of subjects diagnosed with hemophilia B and the study site's ability to conduct a study of this nature.

The Sponsor and Investigator must comply with all applicable regulations. In addition, the Investigator must follow local and institutional requirements including, but not limited to, study agent, clinical research, informed consent, and IRB/IEC regulations. The Sponsor will provide notification to the Investigator of protocol and amendment approvals by regulatory authorities, if applicable.

The sponsor will bear the cost of medical management of SAEs assessed as related to RIXUBIS therapy

Except where the Investigator's signature is specifically required, it is understood that the term "Investigator" as used in this observational protocol and on CRFs refers to the Investigator or appropriate study personnel that the Investigator designates to perform a certain duty. The Investigator is ultimately responsible for the conduct of all aspects of the surveillance. Sub-Investigators or other appropriate study personnel are eligible to sign for the Investigator on designated case report forms.

The Investigator and study coordinator will provide the Sponsor notification of relocation to another institution.

18. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Prior to enrollment of subjects into this study, the approved protocol and the informed consent form will be send for notification, or approval, to the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), in accordance with local requirements. Where applicable, the IRB/IEC letter of notice/approval of the protocol will be signed by the chairperson or recording secretary of the IRB/IEC prior to the start of this study and a copy will be provided to the Sponsor. Notification of the IRB/IEC's composition or a statement that the IRB meets regulatory criteria for the composition of such an IRB/IEC will be provided to the Sponsor.

Should amendments to the protocol be required, the Sponsor will write the amendments in a standard format and provide them to the Investigator for submission to the IRB/IEC.

19. INFORMED CONSENT

Investigators will choose subjects in accordance with the eligibility criteria detailed in Section 7. All subjects or their legally authorized representative or family member (in case of study participants <18 years of age) must sign an informed consent form before entering the study.

Prior to the study, subjects and/or their legally authorized representative(s) will receive a comprehensive explanation of the nature and purpose of the study, and the other elements that are part of obtaining proper informed consent. Subjects or their legally authorized representative(s) will be allowed sufficient time to consider participation in this study, after having the nature of the surveillance explained to them. The consent form must not include any exculpatory statements. It will be reviewed by the IRB/IEC prior to use, where required.

The Sponsor will provide the Investigator in writing any new information that significantly bears on the subjects' risk to receive RIXUBIS. This new information will be communicated by the Investigator to subjects that consent to participate in the study in accordance with IRB/IEC requirements. The informed consent will be updated, if necessary. By signing the informed consent form, subjects (or legally authorized representative(s)) agree that they will complete all evaluations and documentation required by the surveillance, unless they withdraw voluntarily or are terminated from the study for any reason. Every attempt will be made to protect subjects' rights to privacy within legal limits. However, records associated with subjects' participation in the study, including medical histories (case histories) which may identify the subject, and the informed consent signed by the subject will be made available for inspection on request by the Institutional Review Board or Independent Ethics Committee, Baxalta, or designee, the Drug Controller General of India (DCGI), and state and other local authorities. In addition, the results of treatment and laboratory data may be published for scientific purposes, but subjects' identity will not be disclosed.

20. STUDY RECORDS AND CASE REPORT FORMS

20.1 Protocol Interpretations

Questions or interpretations of the protocol or case report forms will be referred to the Sponsor. The Sponsor is responsible for providing interpretation of all data questions.

20.2 Study Records

During the study, the Investigator will maintain complete and accurate documentation for the study, including medical records, records detailing the progress of the study for each subject, laboratory reports, CRFs, signed informed consent forms, correspondence with the IRB/IEC and the study monitor/Sponsor, adverse event reports and information regarding subject screening, enrollment, discontinuation, and completion of the study.

20.3 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as “source data” (see Section 8.1), records detailing the progress of the study for each subject, signed ICFs, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

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

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. The data will be recorded on paper, and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (Section 20).

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

20.4 CONFIDENTIALITY

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the Sponsor.

20.5 RETENTION OF DATA

The Investigator will maintain all records pertaining to this study for a minimum of five years after study end, or up to the maximum period required by local law. The Investigator will obtain permission from the Sponsor in writing before destroying any study records and the Sponsor will notify the Investigator in writing when study records can be destroyed.

21. STUDY MONITORING

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

22. RESPONSIBILITIES

Baxalta will act as the responsible sponsor for the initiation, conduct, reports and publications of the study.

23. APPENDICES

23.1 Study Data and Reporting Schedule

Table 1 Study Data and Reporting Schedule

Study Items	Visits Collected
Informed Consent[a]	Baseline Only
From Physician/Clinical Records	
Eligibility Criteria	Baseline Only
Subject baseline data	Baseline Only
Subject medical history	Baseline Only
Treatment History	Baseline Only
Current/Prescribed RIXUBIS treatment	All Visits
Clinical & Other Data	All Visits
Adverse Events[b]	All Visits
Inhibitor to RIXUBIS[c]	All Visits
RIXUBIS clotting assay[d]	All Visits
Hemostatic Effectiveness	All Visits
From Subject Diary	
Adverse Events[b]	All Visits
Assessment of Hemostatic Effectiveness	All Visits
RIXUBIS Use	All Visits
End of Study Form	Last Visit Only

[a] Occurs at enrollment

[b] AEs will be collected whenever they occur after informed consent is obtained. Each AE will be evaluated by the investigator for seriousness, severity and causal relationship in the assessment of safety (See Definitions in Section 11

[c] Standard procedure according to routine clinical practice

[d] As needed

23.2 Assessment of effectiveness

Total number (%) of treated bleeds and their corresponding hemostatic effectiveness ratings using an "excellent-to-none" 4-point Likert scale by the subjects/care-giver (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.

Table 2 Overall Effectiveness Assessment for On-Demand Treatment	
Excellent	Full relief of pain and cessation of objective signs of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) within approximately 6 hours to 12 hours and after 1 or 2 infusions. No additional infusion is required for the control of bleeding. Any additional infusion for treatment of bleeding will preclude this rating. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding within approximately 6 hours to 24 hours requiring more than 2 infusions for complete resolution. Administration of further infusions to maintain hemostasis would not affect this scoring.
Moderate	Probable and/or slight relief of pain and slight improvement in signs of bleeding within approximately 6 hours to 24 hours. Requires multiple infusions for complete resolution.
None[ii]	No improvement of signs or symptoms or conditions worsen.

Table 3 Overall Effectiveness Assessment for Prophylaxis Therapy	
Excellent	Definitely low bleeding rate with improvement in daily activities and quality of life. Very satisfied with the treatment and worth being continued
Good	Relatively low bleeding rate with some improvement in daily activities and quality of life. Satisfied with the treatment and worth being continued
Moderate	Relative increase in breakthrough bleeding episodes with only partial benefit in terms of activity level and quality of life. Partially satisfied with the treatment. Not sure if it is worth continuing treatment
None[ii]	Frequent breakthrough bleeding episodes interfering with activity level and quality of life. Not satisfied with the treatment.

[ii] If checked, the investigator should determine whether it is considered as "lack of effect" and, if yes, it should be considered as AE

24. REFERENCES

1. Puetz J, Soucie JM, Kempton CL, Monahan PE, Hemophilia Treatment Cenrter Network Investigators. Prevalent inhibitors in haemophilia B subjects enrolled in the Universal Data Collection database. Haemophilia. 2014;20:25-31.

2. World Federation of Hemophilia. Report on the Annual Global Survey, 2014. 52. 2015. Montreàl, Quebec, Canada, World Federation of Hemophilia (WFH).
Link to Publisher´s Site: http://www1.wfh.org/publications/files/pdf-1627.pdf

3. 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:e91-e94.

4. Stonebraker JS, Bolton-Maggs PHB, Brooker M, Farrugia A, Srivastava A. A study of reported factor IX use around the world. Haemophilia. 2011;17:446-455.

5. World Federation of Hemophilia Treatment Guidelines Working Group. Guidelines for the management of hemophilia 2nd Edition. 80. 2012. Montreàl, Quebec, Canada, World Federation of Hemophilia (WFH).
Link to Publisher´s Site: http://www1.wfh.org/publication/files/pdf-1472.pdf

25. SUMMARY OF CHANGES

PROTOCOL 251602

AMENDMENT 1 Version: 2016 SEP 15

Replaces: Original 2016 APR 25

In this section, changes from the previous version of the Protocol, dated 2016 APR 25, are described and their rationale is given.

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

2. Tittle page
   Description of Change: changed "Original" to "Amendment 1: 2016 SEP 15" and added replaces Original
   Purpose for Change: Editorial

3. Section 3: Synopsis
   Description of Change: Deleted "until the end of study" and added "for 2,5 years and followed up for 6 months"
   Purpose for Change: Clarity

4. Section 5: Abbreviations
   Description of Change: changed "WHF" to "WFH and World Federation of Hemophilia"
   Purpose for Change: Editorial

5. Section 6: Introduction
   Description of Change: changed "WHF" to "WFH and World Federation of Hemophilia"
   Purpose for Change: Editorial

6. Section 7.1: Primary objective
   Description of Change: Deleted "list describing adverse events" replaced with "all serious and non-serious adverse events, regardless of causality or expectedness, occurring coincident with use of RIXUBIS will be collected"
   Purpose for Change: Clarity

7. Section 9: Study Design
   Description of Change: Deleted "Of note, if 25 subjects are successfully enrolled before the end of study period, enrollment would continue until the end of study "
   Purpose for Change: To clarify study size.

   Description of Change: Added "Data for the assessment of safety and efficacy" and "to the physicians' office"
   Purpose for Change: Clarity

8. Section 10: Study Duration.
   Description of Change: Added "The follow-up period for each enrolled patient will be up to 6 months from first Physician visit after while on treatment. This shall be documented in at least 3 data collection points (first Physician visit after enrolment, 1 month and 6 months). This period of follow-up is deemed adequate as most patients on prophylaxis will receive RIXUBIS twice weekly equaling 52 doses during the follow-up period. Additionally, for the control and prevention of bleeding episode, patient could receive RIXUBIS for up to 10 days depending on the type of bleeding episode. Given our knowledge of the pharmacokinetics and safety profile of RIXUBIS, we believe hemostatic effectiveness can be assessed and any safety issues identified during the 6-month follow-up period"
   Purpose for Change: To clarify the follow up period.

9. Section 11: Study Procedures.
   Description of Change: Added, "The physician is expected to follow standard clinical practice. The study aims to characterize the safety and describe haemostatic effectiveness of RIXUBIS when used under standard clinical practice of treating hemophilia B patients in India" and "It" and "done in routine clinical care and those" and "and safety"
   Purpose for Change: To clarify the Study Procedures

10. Section 11.1: Initiation & Baseline Visit
    Description of Change: changed "Inhibitor titer" to "Inhibitor titer/Inhibitor screening test"
    Purpose for Change: To clarify subject baseline data

11. Section 11.2: Visit information
    Description of Change: Deleted "please specify"
    Purpose for Change: To clarify the section

12. Section 11.2: Assessment of Safety
Description of Change: changed "Safety" to "Assessment of Safety" deleted sub-section "incidence of non-serious adverse events coincident with RIXUBIS" and "progression" changed sub-section "Other serious adverse events" to "Other serious and non-serious adverse events"
Purpose for Change: To clarify the section

13. Section 11.2: Assessment of Haemostatic Effectiveness
Description of Change: changed "Hemostatic Effectiveness" to "Assessment of Haemostatic Effectiveness"
Purpose for Change: To clarify the section

14. Section 11.3: Last Visit
Description of Change: Added to visit information"Inhibitor titer/Inhibitor screening test" and "Assessment of Safety and Haemostatic Effectiveness" deleted from end of study reason "please specify' and added "(details in section 14)"
Purpose for Change: To clarify the section

15. Section 11.3.1.2: Subject identification code
Description of Change: Corrected error in protocol number from "251501" to "251602"
Purpose for Change: Correction of error

16. Section 11.4.1.1: FIX Inhibitor testing
Description of Change: Added "Patients on RIXUBIS therapy should be screened for inhibitor development at the beginning and at end of study (the intermediate time points is at the discretion of the treating Physicians) and in accordance with the WFH Guidelines as follows [5]:

- Confirmation of the presence of an inhibitor and quantification of the titre is performed in the laboratory, preferably using the Nijmegen-modified Bethesda assay.
- For children, inhibitors should be screened once every five exposure days until 20 exposure days, every 10 exposure days between 21 and 50 exposure days, and at least two times a year until 150 exposure days.
- For adults with more than 150 exposure days, apart from a 6-12 monthly review, any failure to respond to adequate factor concentrate replacement therapy in a previously responsive patient is an indication to assess for an inhibitor.

- Inhibitor measurement should also be done in all patients who have been intensively treated for more than five days, within four weeks of the last infusion.
- Inhibitors should also be assessed prior to surgery or if recovery assays are not as expected, and when clinical response to treatment of bleeding is sub-optimal in the post-operative period."

Purpose for Change: To revise the section per DCGI request

17. Section 12.4: Disease/Study Specific AE Considerations
Description of Change: Added "The sponsor will bear the cost of medical management of SAEs assessed as related to RIXUBIS therapy."
Purpose for Change: To revise the section per DCGI request

18. Section 14: Study Completion
Description of Change: Added "The sponsor will bear the cost of medical management of SAEs assessed as related to RIXUBIS therapy."
Purpose for Change: To revise the section per DCGI request

19. Section 14: Obligations of The Sponsor and The Investigator
Description of Change: Added "The sponsor will bear the cost of medical management of SAEs assessed as related to RIXUBIS therapy."
Purpose for Change: To revise the section per DCGI request

20. Section 23.1: Study Data and Reporting Schedule
Description of Change: Changed "Hemostatic Effectiveness" to "Assessment of Hemostatic Effectiveness" and added "in the assessment of safety" to footnote [(b)]
Purpose for Change: To clarify the section.

21. Section 24: References
Description of Change: Added "World Federation of Hemophilia. Guidelines for the Management of Hemophilia, 2nd edition, 2012. Montreàl, Quebec, Canada, World Federation of Hemophilia (WFH).
Link to Publisher´s Site: http://www1.wfh.org/publications/files/pdf-1472.pdf."
Purpose for Change: Additional reference per DCGI request

INVESTIGATOR ACKNOWLEDGEMENT

RIXUBIS Coagulation Factor IX (Recombinant)
(NONACOG GAMMA)

A Post Marketing Surveillance (PMS) study of RIXUBIS in India

Short Title: RIXUBIS PMS India
(RIXUBIS PMS)

PROTOCOL NUMBER: 251602

AMENDMENT 1: 2016 SEP 15

REPLACES ORIGINAL: 2016 APR 25

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

Signature of Principal Investigator Date

Print Name of Principal Investigator

OBSERVATIONAL STUDY PROTOCOL

RIXUBIS Coagulation Factor IX (Recombinant)

(NONACOG GAMMA)

A Post Marketing Surveillance (PMS) study of RIXUBIS in India

Short Title: RIXUBIS PMS India

(RIXUBIS PMS)

PROTOCOL NUMBER: 251602

ORIGINAL: 2016 APR 25

Study Sponsor(s): **Baxalta Innovations GmbH**
Industriestrasse 67
A-1221 Vienna, AUSTRIA

1. STUDY PERSONNEL

Authorized Representative (Signatory)	Sponsor's Medical Expert
Baxalta Innovations GmbH	[redacted], MD
Industriestrasse 67	[redacted] Global Clinical Development
A-1221 Vienna, AUSTRIA	Baxalta Innovations GmbH

1.1 Study Organization

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

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the Ethics Committees. For information on the definition and assessment of adverse events (AEs), refer to Section 12.5.

ALL SAEs ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE MAH WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT

See SAER form for contact information.

Further details are also available in the study team roster.

NON-SERIOUS ADVERSE EVENT REPORTING

Any non-serious adverse events (AEs), all therapies/procedures to treat the AEs, and the outcome of the AEs are to be reported to the MAH on the appropriate case report forms (CRFs) within 5 business days.

ADVERSE EVENT DEFINITIONS AND ASSESSMENT

For information on the definitions and assessment of these events refer to: definitions of AE in Section 12.1.1, SAE in Section 12.1.2 and assessment of AEs in Section 12.5.

3. SYNOPSIS

Observational Study Number	**251602**
Study Title	A Post Marketing Surveillance (PMS) study of RIXUBIS in India
Dates of Study	Enrollment will start within 3 months after commercial RIXUBIS is available for general use (expected to take place approximately on 31 JAN 2017). Patients will be enrolled until the study end date The expected study completion date is approximately 30 JAN 2020.
Objectives	*Primary objective* To characterize the safety of RIXUBIS when used under standard clinical practice in India. *Secondary objectives* To describe hemostatic effectiveness in subjects receiving RIXUBIS under standard clinical practice in India.
Active Ingredient(s)	Recombinant Factor IX (FIX)
Medicinal Product	Recombinant Factor IX (RIXUBIS)
Study Design	Multi-center, prospective observational non-interventional post-marketing study with no mandated treatments (refer to RIXUBIS PI), visits or assessments.
Treatment(s)	All subjects enrolled will be treated with RIXUBIS according to a regimen determined by the study site treating physician/investigator (i.e., on-demand treatment, prophylaxis treatment, and perioperative treatment).
Duration of Participation	Duration of study will be 36 months.

Subjects	The target enrollment is up to 25 subjects. Patients with congenital hemophilia B (FIX level ≤5%) who have been prescribed RIXUBIS according to the investigator's judgment shall be included as subjects if 1. The patient or legally authorized representative or family member (in case of study participants <18 years of age) gave written informed consent to participate in the study 2. The patient is indicated for treatment according to the RIXUBIS Indian product leaflet. According to the product label, the following patients should not be treated with RIXUBIS and therefore should be excluded from participation in this study if there is: 1. Known hypersensitivity or presence of any contraindication to RIXUBIS or its excipients including hamster protein.
Statistical Analysis:	All analyses will be descriptive and include arithmetic means, medians, standard deviations, minimum, maximum, 25th and 75th percentiles, frequency counts, proportions, and 95% confidence intervals of select point estimates.

4. TABLE OF CONTENTS

Tables

Figures

5. ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event (or Adverse Experience)
BU	Bethesda Units
CHO	Chinese Hamster Ovary
CRF	Case Report Form
DCGI	Drug Controller General of India
ED	Exposure Day
EFAS	Effectiveness full analysis set
EU	European Union
FIX	coagulation factor IX
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HTC	Hemophilia Treatment Center
ICF	informed consent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITI	Immune tolerance induction
IU	International Unit
Kg	Kilogram
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
NHR	India National hemophilia registry
SAE	Serious Adverse Event (or Serious Adverse Experience)
SAS	Safety analysis set
SIC	Subject identification code
WHF	World Hemophilia Foundation

6. INTRODUCTION

Hemophilia B is an X chromosome-linked recessive congenital disorder of blood coagulation due to decreased levels or complete lack of factor IX and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma.

Hemophilia B affects 1-2 infants per 50,000 male newborns. In patients with hemophilia B, susceptibility to uncontrolled bleeding is influenced by disease severity defined by the baseline plasma factor levels of >5% to <40% (mild), 1% to 5% (moderate), or <1% (severe). Of the patients with hemophilia B, approximately 26% reported to have mild, 38% had moderate and 36% had severe disease.[1]

According to the World Hemophilia Foundation (WHF) Report on the Annual Global Survey 2014, there were a total of 14,450 cases of hemophilia and 2,281 confirmed cases of hemophilia B in India in 2014.[2] The number of patients with hemophilia B in India who developed inhibitors was not available. Based on data from the WHF from 1998-2006, the mean prevalence of hemophilia B in India was 0.19 per 100,000 males.[3] The India National hemophilia registry (NHR) reports showed 50% 0f diagnosed hemophilia B patients are on factor IX treatment.

The age distribution of Hemophilia B in India is as follows: 3% between 0-4 years, 14% between 5-13 years, 13% between 14-18 years, 34% between 19-44 years and 7% 45+ years; age was unknown for 29% of patients with hemophilia B.[2]

The total IU of Factor IX in 2014 reported to the WHF was 1,226,400 IU, of which 100% was plasma-derived and 0% was recombinant Factor IX. In 2014, the per capita use of factor IX in India was 0.001 IU per capita. The per capita Factor IX use was consistent from the use reported from 1998-2006 (mean 0.001 IU per capita).[4] The average Factor IX use per patient with hemophilia B from 1998 to 2006 was 203 IU in India.[4] Replacement therapy increases the plasma level of factor IX, providing a temporary correction of the factor deficiency and the bleeding tendency.

One of the most serious complications of replacement therapy is the development of inhibitory antibodies against the exogenously applied coagulation factor in as many as 20-30% of patients with severe hemophilia A, and in 1-5% of patients with severe hemophilia B. The risk for inhibitor development to FIX depends on a number of factors relating to the characteristics of the patient, including: the causative FIX gene mutations, family history, ethnicity, intensity of treatment, and the early implementation of prophylactic treatment.

A substantial proportion of patients with FIX inhibitors have high responding, high titer inhibitors [>5 Bethesda units (BU)]. Inhibitor development in hemophilia B is associated with the development of anaphylactic reactions. Immune tolerance induction (ITI) is frequently less successful in these patients and subjects may develop a nephrotic syndrome as a result of ITI.

RIXUBIS (recombinant coagulation factor IX) is a single-chain purified glycoprotein that has 415 amino acids. It is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell line. RIXUBIS is not derived from human blood or plasma products, and its manufacturer does not include animal or human components. RIXUBIS contains no preservatives. Recombinant coagulation factor IX is a single chain glycoprotein that is a member of the serine protease family of vitamin K-dependent coagulation factors.

Recombinant coagulation factor IX is a recombinant DNA-based protein therapeutic which has structural and functional characteristics comparable to endogenous factor IX. Factor IX is activated by factor VIIa/tissue factor complex in the extrinsic pathway and by factor XIa in the intrinsic coagulation pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. This results ultimately in the conversion of prothrombin to thrombin. Thrombin then converts fibrinogen into fibrin, and a clot can be formed.

6.1 Study Rationale

The results derived from the RIXUBIS clinical development program suggest that RIXUBIS is efficacious, has an acceptable safety profile, and well-tolerated in adults and pediatric subjects with severe to moderately severe hemophilia B in a variety of clinical settings.

This study will collect data on RIXUBIS administered to patients with hemophilia B in standard clinical practice and as per product leaflet.

The purpose of this study is to characterize the safety and describe the effectiveness of RIXUBIS in routine clinical practice

6.2 Clinical Efficacy

RIXUBIS is indicated in adults and children with hemophilia B for the control and prevention of bleeding episodes, perioperative management and routine prophylaxis RIXUBIS is licensed in 14 countries and regions; it is safe and well-tolerated in the treatment of moderately severe to severe hemophilia B.

The efficacy and safety of RIXUBIS was evaluated in 3 clinical studies: a pivotal trial, a pediatric trial, and a surgery trial. An additional continuation study is in progress. These studies involved overall 105 previously treated patients with severe to moderately severe hemophilia B. In all bleeds experienced, 85% were treated with 1-2 infusions and 96% rated haemostatic efficacy as excellent or good.

6.3 Safety

There is an identified risk of hypersensitivity reactions [including reactions/antibodies to Chinese Hamster Ovary (CHO) protein] to RIXUBIS. Potential risks include inhibitor formation, lack of effect, thromboembolic events and nephrotic syndrome following attempted immune tolerance induction in haemophila B patients with FIX inhibitors and a history of allergic reactions. RIXUBIS is not indicated for induction of immune tolerance in patients with Hemophilia B and contraindicated in known hypersensitivity to RIXUBIS or its excipients including CHO protein, disseminated intravascular coagulation (DIC) and signs of fibrinolysis. RIXUBIS treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia.

The integrated safety analysis indicated a low (<1%) incidence of adverse drug reactions (ADRs). A total of 337 AEs were reported in 80/99 (80.8%) subjects treated with at least 1 infusion of RIXUBIS. Most of the AEs were non-serious (327/337) and were not related (331/337) to the administration of RIXUBIS. There were no deaths and no subjects developed inhibitory antibodies to FIX and CHO proteins. There were no thrombotic events or severe allergic reactions.

No actions relating to safety have been taken by the marketing authorisation holder, sponsor, regulatory authorities, and data monitoring committees, or ethics committees thus far on RIXUBIS.

7. OBJECTIVES

7.1 Primary objective

To characterize the safety of RIXUBIS when used under standard clinical practice of hemophilia B patients in India. Specifically, data will be collected on the following occurring coincident with use of RIXUBIS:

1. Serious adverse events/adverse drug reactions (including inhibitor formation)
2. Unexpected adverse events
3. Expected adverse drug reactions
4. Non-serious adverse events

7.2 Secondary objective

To describe hemostatic effectiveness in subjects receiving RIXUBIS under standard clinical practice of hemophilia B patients in India.

8. STUDY POPULATION

8.1 Subject Selection Criteria

All patients with hemophilia B who are eligible to receive RIXUBIS in standard clinical practice.

8.2 Inclusion Criteria

Patients with hemophilia B (FIX level ≤5%) who have been prescribed RIXUBIS according to the investigator's judgment shall be included as subjects if:

1. The patient or legally authorized representative or family member (in case of study participants <18 years of age) gave written informed consent to participate in the study and
2. The patient is indicated for treatment according to the RIXUBIS India product label.

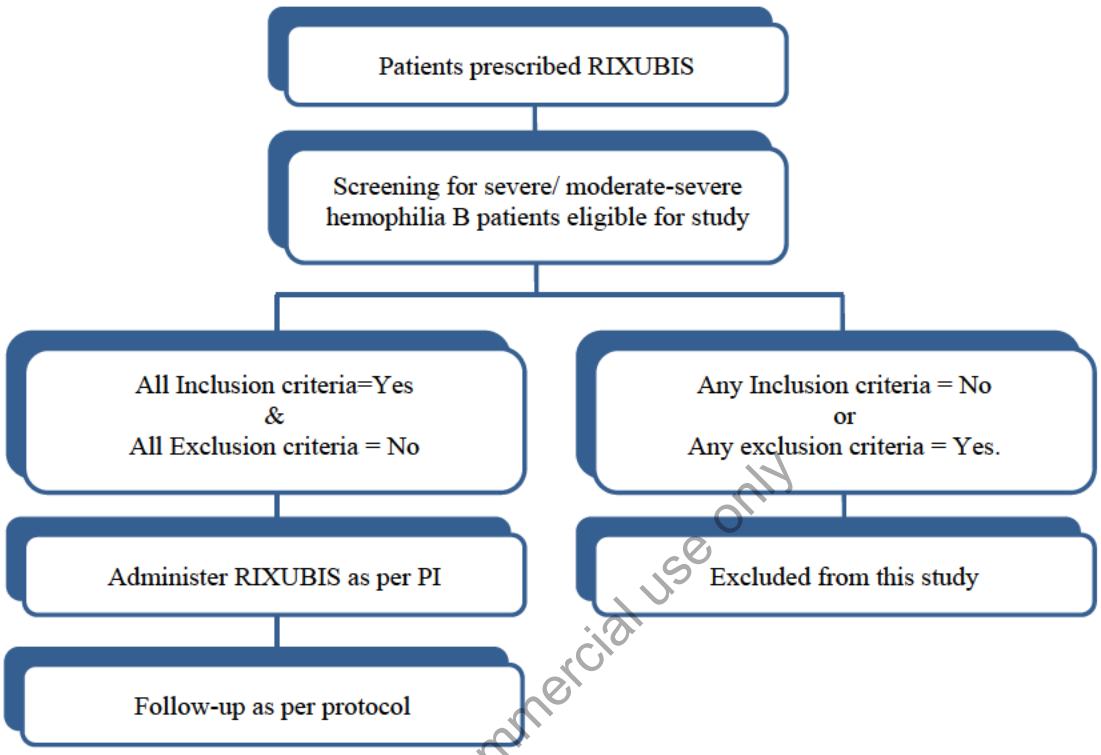
8.3 Exclusion Criteria

According to the product label, the following patients should not be treated with RIXUBIS and therefore should be excluded from participation in this study if there is:

1. Known hypersensitivity or presence of any contraindication to RIXUBIS or its excipients including hamster protein

9. STUDY DESIGN

Figure 1 Study Flow Chart



This is a prospective, uncontrolled, open- label, post-marketing, non-interventional safety surveillance study where the subjects have been prescribed RIXUBIS by their physicians as a choice of therapy. Based on data from the WHF from 1998-2006, the mean prevalence of hemophilia B in India was 0.19 per 100,000 male. In the WHF Report on the Annual Global Survey 2014, 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 in switching patient from current therapy, an estimated study size of 25 subjects will be recruited. The study follows a cohort design, and does not make binding stipulations on treatment schedule. Principally, the study aims to collect subject and treatment-related data of subjects on RIXUBIS therapy over a 36-month period. Of note, if 25 subjects are successfully enrolled before the end of study period, enrollment would continue until the end of study. Informed consent is required to be obtained prior to study enrollment. Eligible patients will be enrolled sequentially to avoid selection bias. Additional data will be collected during subsequent routinely scheduled and unscheduled visits which may occur during routine care.

All study subjects will be included in the assessments of safety and hemostatic effectiveness. The RIXUBIS regimen for this study will be chosen by the attending physician.

9.1 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study that are necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

For additional information on study documentation and CRFs, see Section 20.3

10. STUDY DURATION

The study will start within 3 months after commercial RIXUBIS is available for general use (expected to take place approximately on 31 JAN 2017). The subject is considered enrolled in the study once the informed consent is signed. All data before enrollment (especially with a RIXUBIS treatment) will be collected in the Medical History. The study is expected to last until approximately 30 JAN 2020.

11. STUDY PROCEDURES

The protocol does not stipulate specific clinical or laboratory testing requirements beyond those necessary to establish eligibility. However, certain data will be captured, if available, during the course of the study

11.1 Initiation & Baseline Visit

- **Subject baseline data**
  - Date of visit
  - Date of signed consent
  - Year of birth
  - Age
  - Gender
  - Vital Signs
  - Baseline FIX levels (most recent prior to study enrollment)
  - Inhibitor titer
  - History of thromboembolism
  - Family history of inhibitors
  - Number of bleeding episodes by severity within the last 12 months.
  - Other pertinent medical history
  - Concomitant medications
- **History of inhibitor development**
  - Date(s) of inhibitor detection
  - Total FIX EDs at time of inhibitor detection or, if exact number not available, one of the following ranges: 0, 1-4, 5-20, 21-50, 51-100, 101-150 or >150.
  - FIX product used at the time of inhibitor detection
  - FIX regimen used at the time of inhibitor detection
  - Maximum historical titer
  - Local laboratory cut off value for positive inhibitor titer
  - History of ITI therapy, if any, including FIX product and regimen used

- Date(s) of inhibitor disappearance
- Most recent FIX inhibitor test results.

- **FIX Treatment History**
  - FIX product used prior to RIXUBIS treatment initiation (maximal retrospective time- period of 12 months before enrollment)
  - Name of product, dosage and dosing interval
  - Regimen start and end date
  - Total EDs to FIX products at baseline visit or, where exact number not available, one of the following ranges should be selected: 0, 1-4, 5-20, 21-50, 51-100, 101-150 or >150.

11.2 Every Visit

- **Visit Information**
  - Visit date
  - Visit type (outpatient/office, in-hospital, phone, other – please specify)
  - Reason (scheduled, emergency, other – please specify)
- **Current/Prescribed RIXUBIS treatment**
  - Indication for RIXUBIS (reason(s) for all active prescriptions)
    - Routine prophylaxis
      - Dosage and dosing intervals
      - Regimen start/change date
    - Control of bleeding
      - Type of bleeding episode (minor, moderate, major)
      - Dosage and Duration
      - Number of infusions to treat a bleed
    - Perioperative management
  - Total EDs to RIXUBIS or, where exact number of EDs is not available, one of the following ranges should be selected: 0, 1-4, 5-20, 21-50, 51-100, 101-150 or >150.

- **Clinical & Other Data**
  - Vital signs
  - Bleed occurrence
    - Location
    - Etiology
    - Severity
    - Frequency
    - Number of infusions to treat a bleed
  - Number of bleeds/month/year/ABR score (if available)
  - Postoperative hematomas
    - Dimensions
  - RIXUBIS clotting assay (if performed under routine care)
  - Concomitant medications
  - Non-drug therapies
- **Safety**
  - Inhibitor to RIXUBIS
    - Date(s) of inhibitor detection
    - Date(s) of inhibitor disappearance
    - FIX inhibitor titer(s)
  - Other serious adverse events
    - Event
    - Onset Date
    - Stop Date
    - Severity
    - Progression
    - Outcome
    - Action Taken

- Date of death (if applicable)
- Cause of Death (if applicable)
- Causality assessment by Investigator

➢ Incidence of non-serious adverse events coincident with use of RIXUBIS

- Event
- Onset Date
- Stop Date
- Severity
- Progression
- Outcome
- Action Taken
- Causality assessment by Investigator

- **Hemostatic Effectiveness**
  - ➢ Physician rated effectiveness[i] ("none", "moderate", "good", or "excellent")
  - ➢ Subject rated effectiveness[i]
  - ➢ Number of infusions to treat a bleed (prophylaxis or on demand)

11.3 Last Visit

- **Visit information**
  - ➢ Visit date
  - ➢ Visit type (outpatient/office, in-hospital, phone, other – please specify)
  - ➢ Reason (scheduled, emergency, other – please specify)
- **End of study reason**
  - ➢ Study end, lost to follow-up, death, participant withdrawal, physician decision (specify), other – please specify

[i] Criteria for effectiveness assessment in Appendix, Section 23.2

11.3.1 Subject Inclusion

11.3.1.1 Informed Consent and Enrollment

Any patient who directly, or indirectly through a legally authorized representative, provides informed consent (i.e., signs and dates the informed consent form and assent form, if applicable) is considered enrolled in the study. The study site is responsible for maintaining an enrollment log that includes all subjects enrolled.

11.3.1.2 Subject Identification Code

The following series of numbers will comprise the subject identification code (SIC): protocol identifier, two digit study site number (e.g., 02) to be provided by the MAH, and four digit subject number (e.g., 0003) reflecting the order of enrollment at each site. For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 251501-020003. All study documents pertaining to the subject (e.g., CRFs, clinical documentation, etc.) will be identified with the SIC.

11.4 Clinical Assessments

11.4.1 Medical History, Medications, and Non-Drug Therapies

Medical history, comorbidities and other pre-existing conditions will be reported as available in the patient medical record. Specific data to be obtained is outlined in section 11.1 Findings from any physical examinations pertinent to these data elements should be reported in the CRF.

Hemophilia history and treatment history will be captured, including start and end dates of past treatments where available.

All relevant medications taken and non-drug therapies received from enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

11.4.1.1 FIX inhibitor level

The investigator's assessment of FIX inhibitor level will be recorded on the CRF. The inhibitor assay methods and reference standard used will be reported in the CRF. In the case a positive inhibitor titer is detected, a confirmatory test on a second, separately drawn sample should be performed. This second sample should be taken prior to any change of treatment and shortly (within 1 month) after the previous positive test (a positive inhibitor titer is considered to be ≥ 0.6 BU). For each abnormal FIX inhibitor value, the investigator will determine whether the value is clinically significant or not. For clinically significant values, the investigator will enter as new SAEs (see definition

in Section 12.1.2). If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e. because it is due to a preexisting disease, due to a lab error, or due to another issue that will be specified. Any abnormal value that persists should be followed at the discretion of the investigator.

Any other clinically significant lab abnormality identified through standard clinical practice that meets the criteria for an adverse event (Section 12.1.1) shall be reported.

11.4.1.2 Vital Signs

Vital signs will include height (cm) and weight (kg), if available, at baseline visit or whenever assessed under normal clinical care or clinically significant.

11.5 Treatment with RIXUBIS

The choice of therapeutic approach (prophylaxis vs. on-demand) as well as dose and dosing regimens will be prescribed at the discretion of the investigator. The dosage and number of infusions of RIXUBIS required to achieve adequate hemostasis for each new bleeding episode will be recorded as well as all the RIXUBIS lot numbers. Details pertaining to infusions administered in the context of a home treatment will be sourced from diaries supplied to subjects by the Sponsor. If the subject receives RIXUBIS while undergoing a surgical or invasive procedure, data related to RIXUBIS therapy, effectiveness and safety will be recorded.

If, at any time during the course of the study, a subject's bleed does not respond to therapy with RIXUBIS it is recommended to screen for the presence of an inhibitor (see Section 11.4.1.1). All subjects will be treated at the discretion of the treating physician/investigator until adequate hemostasis is achieved. Additionally, details of concomitant medication used in conjunction with the treatment of all acute bleeding events will be recorded.

11.5.1 Summary Description of RIXUBIS

RIXUBIS (rFIX) is an antihaemophilic factor indicated in adults and children with hemophilia B for:

- Treatment and prevention of bleeding episodes in patients with hemophilia B (congenital factor IX deficiency)
- Routine prophylaxis of bleeding episodes in patients with hemophilia B
- Perioperative management in patients with hemophilia B

RIXUBIS is not indicated for induction of immune tolerance in patients with Hemophilia B.

RIXUBIS (recombinant coagulation factor IX) is a single-chain purified glycoprotein that has 415 amino acids. It is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell line. RIXUBIS is not derived from human blood or plasma products, and its manufacturer does not include animal or human components. RIXUBIS contains no preservatives. Recombinant coagulation factor IX is a single chain glycoprotein that is a member of the serine protease family of vitamin K-dependent coagulation factors.

Recombinant coagulation factor IX is a recombinant DNA-based protein therapeutic which has structural and functional characteristics comparable to endogenous factor IX. Factor IX is activated by factor VIIa/tissue factor complex in the extrinsic pathway and by factor XIa in the intrinsic coagulation pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. This results ultimately in the conversion of prothrombin to thrombin. Thrombin then converts fibrinogen into fibrin, and a clot can be formed.

11.5.1.1 Packaging and Labeling

Please refer to the product label.

11.5.1.2 Shelf-life and Storage

Please refer to the product label.

11.5.1.3 Reconstitution

Please refer to the product label.

11.5.1.4 Routes and Modes of Administration

Please refer to the product label.

11.5.1.5 Dosing Schedule and Requirements

For up to date dosing information, please refer to the product label.

12. ASSESSMENT OF SAFETY

12.1 Definitions of Safety Events

12.1.1 Adverse Event (AE)

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

12.1.2 Serious Adverse Event (SAE)

An SAE is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death).
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above.
    - As pertains to this study, examples of medically important events include, but are not limited to:
        - Thromboembolism/DIC/Fibrinolysis
        - FIX inhibitor development (≥ 0.6 BU)
        - Nephrotic syndrome.

12.1.3 Non-Serious Adverse Event

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

12.1.4 Unexpected Adverse Events

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

12.2 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequelae, which require (prolonged) therapeutic intervention.

12.3 Causality

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

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not related to the RIXUBIS (i.e., does not follow a reasonable temporal relationship to the administration of RIXUBIS or has a much more likely alternative etiology).
- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the RIXUBIS
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of RIXUBIS
  - An alternative etiology is equally or less likely compared to the potential relationship to the RIXUBIS
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of RIXUBIS, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive rechallenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the RIXUBIS as evidenced by measurement of the RIXUBIS concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

12.4 Disease/Study Specific AE Considerations

- Preexisting diseases that are present before entry into the study are described in the medical history, and those that manifest with the same severity, frequency, or duration during the study, will not be recorded as AEs/SAEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF
- Bleeding events will not be considered as AEs if they do not qualify as an SAE. Elective and planned surgeries when these surgeries relate to a preexisting disease (see also Section 12.1.2) that has not worsened during study participation will not be considered as (S)AEs
- Any pregnancy that occurs after maternal or paternal administration of medicinal product will be reported on a Pregnancy Report Form and followed-up at estimated date of delivery and 1 year post-delivery, if feasible. Any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE
- Overdosing, underdosing, abuse and or misuse, withdrawal, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the dosing schedule defined in the package insert). Definition of under- and overdosing is done as per the judgment of the treating physician. Failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

12.5 Assessment of Adverse Events

Each AE, from enrollment until study completion/discontinuation date, will be described on the AE CRF (i.e., 1 AE per form) using the medical diagnosis (preferred), symptom, or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1.1 Each AE, will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.2
- Severity as defined in Section 12.2
- Causal relationship to RIXUBIS exposure as defined in Section 12.3

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal) and action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until the study completion/termination visit.

12.6 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (mild, moderate, or severe as defined in Section 12.2) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All medications taken and non-drug therapies received from enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs

12.7 Assessment of Laboratory Values

12.7.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each abnormal laboratory value is to be recorded on the CRF form. For each abnormal laboratory value, the investigator will determine whether the value is also considered an AE (see definition in Section 12.1.1). If yes, the sign, symptom, or medical diagnosis will be recorded on the AE CRF. If the abnormal value was not deemed an AE because it was due to a lab error, was due to a preexisting disease, was not clinically significant, was a symptom of a new/worsened condition already recorded as an AE, or was due to another issue that will be specified, the treating physician/investigator will record the justification on the CRF form. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

If a FIX inhibitor (Bethesda titer ≥ 0.6 BU) is detected in any subject during the course of the study, the subject may continue on the study at the same or higher dose per infusion at the discretion of the study site treating physician/investigator, pending the outcome of subsequent inhibitor testing as directed by the study site investigator. If a new inhibitor is detected (≥ 0.6 BU), it must be reported as an SAE, and the corresponding SAE page must be completed and returned within 24 hours to the Sponsor (see Section 2).

If a subject tests positive for a FIX inhibitor, a confirmatory test on a second, separately drawn sample should be performed. This second sample should be taken prior to any change of treatment and shortly (within 1 month) after the previous positive test.

For methods of assessment see Section 11.4

13. SUBJECT WITHDRAWAL

Any subject may withdraw from the study for any reason at any time. Additionally, the investigator has the possibility to withdraw any subject from the study at his discretion. The investigator should provide the sponsor with a written account of any reasons for early withdrawal.

14. STUDY COMPLETION

The end-of-study CRF will be completed at study termination. The primary reason for termination will be listed on the CRF. One of the following conditions should be met:

a. Subject completed study.

b. Subject experienced adverse drug reaction(s) from the study drug necessitating discontinuance of treatment.

c. Subject was withdrawn by the primary investigator at the site for non-study drug related reasons.

d. Unsatisfactory therapeutic response to study product (as determined by the investigator).

e. Subject or legally authorized representative voluntarily withdrew consent.

f. Subject was lost to follow- up.

g. Subject died.

h. Other reason for premature study termination.

Regardless of the reason for termination, all data available for the subject up to the time of termination should be recorded onto the appropriate CRF, prior to retrieval by the Sponsor. In the event of premature study termination resulting from an adverse event, clinical and/or laboratory investigations that are beyond the scope of the required study observations may be performed as part of the evaluation of the event at the discretion of the study site investigator.

The physician/investigator shall provide follow-up information on subjects who experienced serious adverse events until a diagnosis and final outcome are established or 30 days after the termination visit whichever is earlier.

15. STATISTICAL ANALYSIS

15.1 Data Analysis Plan

15.1.1 Datasets and Analysis Cohorts

Safety Analysis Set (SAS)

All subjects having received RIXUBIS at any time during the study will be included in the safety analysis set.

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. This dataset will be used for the hemostatic effectiveness assessment.

15.1.2 Methods of Analysis

All analyses will be descriptive and include specifically but not exclusively, arithmetic means, medians, standard deviations, minimum, maximum, 25th and 75th percentiles, frequency counts, proportions and 95% confidence intervals of select point estimates. Figures will be prepared to illustrate the patterns of data over time where appropriate. The number of subjects included in each analysis set will be reported. Analyses will be performed using available data, due to the non-interventional nature of the study, missing values are expected.

16. DATA MANAGEMENT

All AEs that occurred during or after first RIXUBIS infusion will be categorized according to the MedDRA dictionary and summarized by system organ class and preferred term. AEs will be cross-tabulated for relatedness, seriousness, and severity. AEs that occurred before first RIXUBIS infusion will be listed separately. Any subject will be allotted a unique identification number described in Section 11.3.1.2, reflecting the order in which enrollment took place at that site. The subject's unique identification number is required for data allocation and evaluation. All data collected during the study will be entered in an electronic database for statistical analysis. Plausibility checks will be done, and attempts will be made to resolve inconsistencies.

17. OBLIGATIONS OF THE SPONSOR AND THE INVESTIGATOR

This study will be conducted in accordance with this observational protocol, the Declaration of Helsinki, and national regulations applicable to post-authorization surveillance studies.

The Sponsor will select Investigators on the basis of their expertise in the treatment of subjects diagnosed with hemophilia B and the study site's ability to conduct a study of this nature.

The Sponsor and Investigator must comply with all applicable regulations. In addition, the Investigator must follow local and institutional requirements including, but not limited to, study agent, clinical research, informed consent, and IRB/IEC regulations. The Sponsor will provide notification to the Investigator of protocol and amendment approvals by regulatory authorities, if applicable.

Except where the Investigator's signature is specifically required, it is understood that the term "Investigator" as used in this observational protocol and on CRFs refers to the Investigator or appropriate study personnel that the Investigator designates to perform a certain duty. The Investigator is ultimately responsible for the conduct of all aspects of the surveillance. Sub-Investigators or other appropriate study personnel are eligible to sign for the Investigator on designated case report forms.

The Investigator and study coordinator will provide the Sponsor notification of relocation to another institution.

18. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Prior to enrollment of subjects into this study, the approved protocol and the informed consent form will be send for notification, or approval, to the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), in accordance with local requirements. Where applicable, the IRB/IEC letter of notice/approval of the protocol will be signed by the chairperson or recording secretary of the IRB/IEC prior to the start of this study and a copy will be provided to the Sponsor. Notification of the IRB/IEC's composition or a statement that the IRB meets regulatory criteria for the composition of such an IRB/IEC will be provided to the Sponsor.

Should amendments to the protocol be required, the Sponsor will write the amendments in a standard format and provide them to the Investigator for submission to the IRB/IEC.

19. INFORMED CONSENT

Investigators will choose subjects in accordance with the eligibility criteria detailed in Section 7. All subjects or their legally authorized representative or family member (in case of study participants <18 years of age) must sign an informed consent form before entering the study.

Prior to the study, subjects and/or their legally authorized representative(s) will receive a comprehensive explanation of the nature and purpose of the study, and the other elements that are part of obtaining proper informed consent. Subjects or their legally authorized representative(s) will be allowed sufficient time to consider participation in this study, after having the nature of the surveillance explained to them. The consent form must not include any exculpatory statements. It will be reviewed by the IRB/IEC prior to use, where required.

The Sponsor will provide the Investigator in writing any new information that significantly bears on the subjects' risk to receive RIXUBIS. This new information will be communicated by the Investigator to subjects that consent to participate in the study in accordance with IRB/IEC requirements. The informed consent will be updated, if necessary. By signing the informed consent form, subjects (or legally authorized representative(s)) agree that they will complete all evaluations and documentation required by the surveillance, unless they withdraw voluntarily or are terminated from the study for any reason. Every attempt will be made to protect subjects' rights to privacy within legal limits. However, records associated with subjects' participation in the study, including medical histories (case histories) which may identify the subject, and the informed consent signed by the subject will be made available for inspection on request by the Institutional Review Board or Independent Ethics Committee, Baxalta, or designee, the Drug Controller General of India (DCGI), and state and other local authorities. In addition, the results of treatment and laboratory data may be published for scientific purposes, but subjects' identity will not be disclosed.

20. STUDY RECORDS AND CASE REPORT FORMS

20.1 Protocol Interpretations

Questions or interpretations of the protocol or case report forms will be referred to the Sponsor. The Sponsor is responsible for providing interpretation of all data questions.

20.2 Study Records

During the study, the Investigator will maintain complete and accurate documentation for the study, including medical records, records detailing the progress of the study for each subject, laboratory reports, CRFs, signed informed consent forms, correspondence with the IRB/IEC and the study monitor/Sponsor, adverse event reports and information regarding subject screening, enrollment, discontinuation, and completion of the study.

20.3 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as “source data” (see Section 8.1), records detailing the progress of the study for each subject, signed ICFs, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

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

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. The data will be recorded on paper, and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (Section 20).

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

20.4 CONFIDENTIALITY

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the Sponsor.

20.5 RETENTION OF DATA

The Investigator will maintain all records pertaining to this study for a minimum of five years after study end, or up to the maximum period required by local law. The Investigator will obtain permission from the Sponsor in writing before destroying any study records and the Sponsor will notify the Investigator in writing when study records can be destroyed.

21. STUDY MONITORING

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

22. RESPONSIBILITIES

Baxalta will act as the responsible sponsor for the initiation, conduct, reports and publications of the study.

23. APPENDICES

23.1 Study Data and Reporting Schedule

Table 1 Study Data and Reporting Schedule

Study Items	Visits Collected
Informed Consent[a]	Baseline Only
From Physician/Clinical Records	
Eligibility Criteria	Baseline Only
Subject baseline data	Baseline Only
Subject medical history	Baseline Only
Treatment History	Baseline Only
Current/Prescribed RIXUBIS treatment	All Visits
Clinical & Other Data	All Visits
Adverse Events[b]	All Visits
Inhibitor to RIXUBIS[c]	All Visits
RIXUBIS clotting assay[d]	All Visits
Hemostatic Effectiveness	All Visits
From Subject Diary	
Adverse Events[b]	All Visits
Hemostatic Effectiveness	All Visits
RIXUBIS Use	All Visits
End of Study Form	Last Visit Only

[a] Occurs at enrollment

[b] AEs will be collected whenever they occur after informed consent is obtained. Each AE will be evaluated by the investigator for seriousness, severity and causal relationship (See Definitions in Section 11

[c] Standard procedure according to routine clinical practice

[d] As needed

23.2 Assessment of effectiveness

Total number (%) of treated bleeds and their corresponding hemostatic effectiveness ratings using an "excellent-to-none" 4-point Likert scale by the subjects/care-giver (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.

Table 2 Overall Effectiveness Assessment for On-Demand Treatment	
Excellent	Full relief of pain and cessation of objective signs of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) within approximately 6 hours to 12 hours and after 1 or 2 infusions. No additional infusion is required for the control of bleeding. Any additional infusion for treatment of bleeding will preclude this rating. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding within approximately 6 hours to 24 hours requiring more than 2 infusions for complete resolution. Administration of further infusions to maintain hemostasis would not affect this scoring.
Moderate	Probable and/or slight relief of pain and slight improvement in signs of bleeding within approximately 6 hours to 24 hours. Requires multiple infusions for complete resolution.
None[ii]	No improvement of signs or symptoms or conditions worsen.

Table 3 Overall Effectiveness Assessment for Prophylaxis Therapy	
Excellent	Definitely low bleeding rate with improvement in daily activities and quality of life. Very satisfied with the treatment and worth being continued
Good	Relatively low bleeding rate with some improvement in daily activities and quality of life. Satisfied with the treatment and worth being continued
Moderate	Relative increase in breakthrough bleeding episodes with only partial benefit in terms of activity level and quality of life. Partially satisfied with the treatment. Not sure if it is worth continuing treatment
None[ii]	Frequent breakthrough bleeding episodes interfering with activity level and quality of life. Not satisfied with the treatment.

[ii] If checked, the investigator should determine whether it is considered as "lack of effect" and, if yes, it should be considered as AE

24. REFERENCES

1. Puetz J, Soucie JM, Kempton CL, Monahan PE, Hemophilia Treatment Cenrter Network Investigators. Prevalent inhibitors in haemophilia B subjects enrolled in the Universal Data Collection database. Haemophilia. 2014;20:25-31.

2. World Federation of Hemophilia. Report on the Annual Global Survey, 2014. 52. 2015. Montreàl, Quebec, Canada, World Federation of Hemophilia (WFH). Link to Publisher´s Site: http://www1.wfh.org/publications/files/pdf-1627.pdf

3. 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:e91-e94.

4. Stonebraker JS, Bolton-Maggs PHB, Brooker M, Farrugia A, Srivastava A. A study of reported factor IX use around the world. Haemophilia. 2011;17:446-455.

INVESTIGATOR ACKNOWLEDGEMENT

RIXUBIS Coagulation Factor IX (Recombinant)

(NONACOG GAMMA)

A Post Marketing Surveillance (PMS) study of RIXUBIS in India

Short Title: RIXUBIS PMS India

(RIXUBIS PMS)

PROTOCOL NUMBER: 251602

ORIGINAL: 2016 APR 25

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

Signature of Principal Investigator Date

Print Name of Principal Investigator