TITLE PAGE –NON-INTERVENTIONAL STUDY INFORMATION

PROTOCOL TITLE	**Post Authorization RIXUBIS Study (PARIXS)**
PROTOCOL ID #	251401
ORIGINAL	20 MAR 2015
EU PAS REGISTER	Study to be registered
MEDICINAL PRODUCT	
Active Ingredient(s)	Recombinant Factor IX (FIX)
Medicinal Product	Recombinant Factor IX (RIXUBIS)
MARKETING AUTHORIZATION HOLDER (MAH)	Baxalta Innovations GmbH, Industriestrasse 67 A-1221 Vienna, Austria
JOINT PASS	No
RESEARCH QUESTION & OBJECTIVES	
Research Question	
The study addresses the description of routine clinical practice with a new rFIX product (RIXUBIS) using any therapeutic regimen administered to hemophilia B patients. This post-authorization, prospective, uncontrolled, observational, open-label, non-interventional, multicenter cohort study is designed to measure short and long-term outcomes in terms of effectiveness, safety, joint health, quality of life and economic outcomes in routine clinical practice.	
Primary Objective	
To assess hemostatic effectiveness in the prevention of bleeding events in subjects with hemophilia B receiving rFIX (RIXUBIS) using any therapeutic regimen in routine clinical practice.	
Secondary Objective(s)	

• To describe hemostatic effectiveness in the treatment of bleeding events in subjects with hemophilia B receiving rFIX (RIXUBIS).
• To describe the safety and immunogenicity in subjects with hemophilia B receiving rFIX (RIXUBIS).
• To describe joint health outcomes in subjects receiving rFIX (RIXUBIS).
• Health-Related Quality of Life (HR-QoL) objectives:
  ➢ To describe HR-QoL in subjects receiving rFIX (RIXUBIS)
  ➢ To describe acute and chronic pain associated with hemophilia in subjects receiving rFIX (RIXUBIS)
  ➢ To describe the physical activity in subjects receiving rFIX (RIXUBIS)
• To describe hemophilia-related comorbidity in subjects receiving rFIX (RIXUBIS)
• To describe healthcare resource use in subjects receiving rFIX (RIXUBIS) on-demand or prophylactically	

COUNTRY(-IES) OF STUDY	Germany, with the option to expand to other countries

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MARKETING AUTHORIZATION HOLDER(S)

MAH	Baxalta Innovations GmbH, Industriestrasse 67 A-1221 Vienna, Austria
MAH CONTACT PERSON	Barbara Valenta-Singer, MD Vice President Global Clinical Development Baxalta Innovations GmbH

SERIOUS ADVERSE EVENT REPORTING

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

ALL SAEs ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE MAH WITHIN 24 HOURS AFTER 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 11.1.1, and assessment of AEs in Section 11.1.2, SAE in Section 11.1.1.1,

1. TABLE OF CONTENTS

Tables

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ABR	Annualized bleeding rate
AJBR	Annualized joint bleeding rate
aPTT	Activated partial thromboplastin time
AUC	Area under the curve
BU	Bethesda Unit
BW	Body weight
BP	Bodily pain
CHO	Chinese hamster ovary
CRF	Case report form
DIC	Disseminated intravascular coagulation
EC	Ethics committee
e-CRF	Electronic case report form
ED	Exposure day(s)
EFAS	Effectiveness Full Analysis Set
ESODPT	Effectiveness of switch from on demand to prophylaxis
ER	Emergency room
EQ-5D	EuroQol Five Dimension
EQ-5D-Y	EuroQol Five Dimension Youth version
FISH	Functional Independence Score in Hemophilia
FVIII	Factor VIII
FIX	Factor IX
FSI	First subject in
GH	General Health
GPV	Global Pharmacovigilance
HAL	Hemophilia Activity List
HJHS	Hemophilia Joint Health Score
HRQoL	Health-Related Quality of Life
HRQoL AS	Health-Related Quality of Life analysis set
HRUR	Health resource use related
ICF	Informed consent form
IP	Investigational product
IR	Incremental recovery
ITI	Immune tolerance induction
IU	International unit
JHFAS	Joint Health/Function analysis set
LSO	Last subject out

Abbreviation	Definition
MBR	Monthly bleed rate
MRI	Magnetic reasonance imaging
MAH	Marketing authorization holder
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
NMC	Non-medical complaint
NRS	Numerical rating scale
NSAE	Non-serious adverse event
PEAS	Pharmacoeconomic analysis set
PedHAL	Pediatric Hemophilia Activity Level
PCS	Physical Component Summary
PD	Pharmacodynamics, Pharmacodynamic
PHS	Physical Summary (SF-10)
PK	Pharmacokinetics, Pharmacokinetic
PSS	Psychosocial Summary (SF-10)
PSUR	Periodic Safety Update Report
PTP	Previously treated patient
PUP	Previously untreated patient
QoL	Quality of life
RoM	Range of motion
RP	Role Physical
SAE	Serious adverse event
SAER	Serious adverse event report
SAP	Statistical analysis plan
SAS	Safety analysis set
SIC	Subject identification code
SF	Social Functioning
SF-10	Short-Form-10 Health Survey
SF-12	Short-Form-12 Health Survey
SF-36	Short-Form-36 Health Survey
T1/2	Half-life
TAE	Thrombotic adverse event
VAS	Visual Analog Scale
vs.	Versus
VT	Vitality
WFH	World Federation of Hemophilia
WHO	World Health Organization

3. RESPONSIBLE PARTIES
AUTHORIZED REPRESENTATIVE (SIGNATORY) / RESPONSIBLE PARTY

3.1 MAH's Authorized Representative (Signatory)

Barbara Valenta-Singer, MD
Vice President, Clinical Development
Baxalta Innovations GmbH

3.2 Investigators

The names and contact information of all investigators will be maintained by the MAH in a separate file and provided to the individual investigators (see Annex 14.1).

3.3 Other Individuals Involved in the Study

The names and contact information of other individuals involved with the study (eg, MAH's medical expert, MAH's representative(s), laboratories, steering committees, and oversight committees (including ethics committees [ECs]), as applicable) will be maintained by the MAH and provided to the investigators (see Annex 14.1).

4. ABSTRACT

Title: Post Authorization RIXubis Study (PARIXS)

Rationale and background: The results derived from the RIXUBIS clinical development program suggest that RIXUBIS is efficacious, safe, and well-tolerated in adults and pediatric subjects with severe to moderately severe hemophilia B in a variety of clinical settings [1;2;3].

Research question and objectives:
This study will collect data on a new product rFIX (RIXUBIS) using any therapeutic regimens administered to patients with hemophilia B in routine clinical practice.

The purpose of this study is to measure short and long-term outcomes in terms of effectiveness, safety, joint health and quality of life in routine clinical practice.
The primary objective aims to describe hemostatic effectiveness in the prevention of bleeding events in subjects with hemophilia B receiving rFIX (RIXUBIS) using any therapeutic regimen in routine clinical practice.

The secondary objectives focus on a) the description of the hemostatic effectiveness in the on-demand treatment of bleeding events, and b) safety, immunogenicity, joint-health outcomes,quality of life outcomes including acute and chronic pain and hemophilia B-related co-morbidity, physical activity and health care resources used by subjects receiving rFIX (RIXUBIS) using any therapeutic regimen in routine practice.

Study design: This study is a post-authorization, prospective, uncontrolled, non-interventional, multicenter cohort study to describe the short and long-term effectiveness, safety, immunogenicity, joint health, QoL and pain outcomes, and healthcare resource utilization in subjects with hemophilia B receiving rFIX (RIXUBIS) using any therapeutic regimen, in routine clinical practice.

Population: All patients with congenital hemophilia B receiving RIXUBIS in routine clinical practice. The observation period for each enrolled subject will be 4 years.

Variables: Effectiveness of prophylaxis, effectiveness of on demand treatment, safety and immunogenicity, joint health outcomes, health related quality of life questionnaires, acute and chronic pain assessment, assessment of physical activity, economic variables and comorbidities will be assessed.

Data sources: Data sources are patient's original clinical records and the patient's diary.

Study size: As no hypothesis testing or interval estimation will be applied, the sample size for the study is not based on statistical considerations. The sample size of approximately 80 evaluable subjects was selected as a reasonable number for a non-interventional study to recruit in Germany within the enrollment period planned for the study. Sample size could increase as other countries may participate in this study.

5. AMENDMENTS AND UPDATES

Original: 20 MAR 2015

6. MILESTONES

Milestone	Planned Date
Final protocol submission	TBD
Registration in EU PAS Register	TBD
Start of data collection	30 APR 2015
End of data collection	31 DEC 2021
Regular Study Progress Reports and Safety Reviews	To be scheduled
Final Report of Study Results	30 JUN 2022

7. RATIONALE AND BACKGROUND

7.1 Medicinal Product Safety Profile

RIXUBIS [Coagulation Factor IX (Recombinant)] is a sterile white lyophilized powder and solvent for intravenous injection available in single-use vials containing nominally 250, 500, 1000, 2000 and 3000 international units. Each kit contains a single-use vial containing the lyophilized powder (Coagulation FIX) with indicated potency, 5mL of sterile water for injection (solvent) and a BaxJect II device. RIXUBIS is produced in Chinese Hamster Ovary (CHO) cells without exposure to proteins of human or animal origin. In addition, two viral inactivation steps (solvent/detergent treatment and 15nm nanofiltration) are performed. RIXUBIS is indicated for the treatment and prophylaxis of bleeding in patients with hemophilia B (congenital factor IX deficiency). Dosage and frequency of administration should always be guided by the clinical effectiveness in each individual case.

Treatment should be under the supervision of a physician experienced in the treatment of hemophilia.

Posology

The dose and duration of the substitution therapy depends on the severity of the factor IX deficiency, on the location and extent of the bleeding, and on the patient's clinical condition, age and pharmacokinetic (PK) parameters of factor IX, such as incremental recovery (IR) and half-life (T1/2).

During the course of treatment, appropriate determination of factor IX levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to factor IX, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in severely underweight or overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor IX activity) is vital.

To ensure that the desired factor IX activity plasma level has been attained, careful monitoring using an appropriate factor IX activity assay is advised and, if necessary, appropriate adjustments to the dose and the frequency of repeated infusions should be performed. When using an *in vitro* thromboplastin time (aPTT)-based one stage clotting assay for determining factor IX activity in patients' blood samples, plasma factor IX activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. This is of particular importance when changing the laboratory and/or reagents used in the assay.

The number of units of factor IX administered is expressed in International Units (IU), which are related to the current World Health Organization (WHO) standard for factor IX products. Factor IX activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to an International Standard for factor IX in plasma).

One International Unit (IU) of factor IX activity is equivalent to that quantity of factor IX in one milliliter of normal human plasma.

On-demand treatment

The calculation of the required dose of factor IX is based on the empirical finding that 1 International Unit (IU) factor IX per kg body weight raises the plasma factor IX activity by 0.9 IU/dL (range from 0.5 to 1.4 IU/dL) or 0.9% of normal activity in patients aged 12 years and older (for further details, .

The required dose is determined using the following formula:

Patients aged 12 years and older

Required units =	body weight (kg)	x	desired factor IX rise (%) or (IU/dL)	x	reciprocal of observed recovery (dL/kg)	

For an incremental recovery of 0.9 IU/dL per IU/kg, the dose is calculated as follows:

Required units =	body weight (kg)	x	desired factor IX rise (%) or (IU/dL)	x	1.1 dL/kg

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in each individual case.

In the case of the following hemorrhagic events, the factor IX activity should not fall below the given plasma activity level (in % of normal or IU/dL) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

Degree of hemorrhage/Type of surgical procedure	Factor IX level required (%) or (IU/dL)	Frequency of doses (hours)/Duration of therapy (days)
Hemorrhage Early hemarthrosis, muscle bleeding or oral bleeding	20 – 40	Repeat every 24 hours. At least 1 day, until the bleeding episode, as indicated by pain, resolves or healing is achieved.
More extensive hemarthrosis, muscle bleeding or hematoma	30 – 60	Repeat infusion every 24 hours for 3–4 days or more, until pain and acute disability are resolved.
Life-threatening hemorrhages.	60 – 100	Repeat infusion every 8 to 24 hours until threat is resolved.
Minor Surgery Minor surgery including tooth extraction	30 – 60	Every 24 hours, at least 1 day, until healing is achieved.
Major surgery	80 – 100 (pre- and postoperative)	Repeat infusion every 8 to 24 hours until adequate wound healing occurs, then provide therapy for at least another 7 days to maintain a factor IX activity of 30% to 60% (IU/dl).

Careful monitoring of replacement therapy is especially important in cases of major surgery or life-threatening hemorrhages.

Prophylaxis

For long-term prophylaxis against bleeding in patients with severe hemophilia B, the usual doses are 40 to 60 IU of factor IX per kilogram of body weight at intervals of 3 to 4 days for patients aged 12 years and older. In some cases, depending upon the individual patient's pharmacokinetics (PK), age, bleeding phenotype and physical activity, shorter dosage intervals or higher doses may be necessary.

Continuous infusion

Do not administer RIXUBIS by continuous infusion.

Pediatric population

On-demand treatment:

The calculation of the required dose of factor IX is based on the empirical finding that 1 IU factor IX per kg body weight raises the plasma factor IX activity by 0.7 IU/dL (range from 0.31 to 1.0 IU/dL) or 0.7% of normal activity in patients under 12 years of age .

The required dosage is determined using the following formula:

Patients under 12 years of age:

$$\text{Required units} = \text{body weight (kg)} \times \text{desired factor IX rise (\%) or (IU/dL)} \times \text{reciprocal of observed recovery (dL/kg)}$$

For an incremental recovery of 0.7 IU/dL per IU/kg, the dose is calculated as follows:

$$\text{Required units} = \text{body weight (kg)} \times \text{desired factor IX rise (\%) or (IU/dL)} \times 1.4 \text{ dL/kg}$$

The same table as for adults can be used to guide dosing and frequency of infusions in case of bleeding episodes and surgery (see above).

Prophylaxis:

The recommended dose range for pediatricpediatric patients under 12 years of age is 40 to 80 IU/kg at intervals of 3 to 4 days. In some cases, depending upon the individual patient’s PK, age, bleeding phenotype and physical activity, shorter dosage intervals or higher doses may be necessary.

Special precautions for storage

Do not freeze. Store in the original package in order to protect from light. For storage conditions of the reconstituted medicinal product see the RIXUBIS SPC.

Method of administration

Reconstitute the product (see the RIXUBIS Package Insert) and slowly inject or infuse via the intravenous route.

Safety Profile:

Data are based on a total of 99 subjects with exposure to at least 1 infusion of RIXUBIS (1 Pivotal Study, 1 Pediatric Study; 1 ongoing Continuation Study and 1 Surgery Study.

The total consumption in these four studies was 50,756,155 IU of RIXUBIS in 14,018 infusions. The majority of these infusions were administered for prophylaxis (40,172,963 IU administered in 11,504 infusions). Exposure per subject was a median of 156 exposure days (EDs) (range: 8 to 316 EDs), with a median of 163 infusions per subject (range: 8 to 327 infusions) and a median consumption of RIXUBIS of 8201.8 IU/kg (range: 376 to 22,705 IU/kg).

Of the 99 treated subjects, 11 (11.1%) were <6 years of age, 12 (12.1%) were 6 to <12 years of age, 3 (3.0%) were adolescents (12 to <16 years of age), and 73 (73.7%) were adults (16 years of age and older). The majority (86.9%) of subjects were white, 1.0% were black or African American, 5.1% were Japanese, 3.0% were Native Latin American, 2.0% were Mestizo, 1.0% were Arab and 1.0% were Indian.

Safety was assessed in terms of adverse events (AEs) including severe allergic reactions and thrombotic events, immunogenicity (inhibitory and total binding antibodies to FIX, antibody titers to CHO and rFurin), viral safety and thrombotic markers, clinically significant laboratory values (hematology and clinical chemistry) and vital signs.

Overall AEs:
Results of the integrated safety analysis indicated that RIXUBIS is safe and well tolerated, with a low 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 . The majority of AEs were non-serious (327/337) and considered unrelated to the RIXUBIS (331/337). There were no deaths and no subjects developed inhibitory antibodies to FIX. There were no thrombotic events or severe allergic reactions. Two subjects were withdrawn due to an unrelated SAE requiring emergency treatment with another factor IX product (following a road traffic accident in one subject, and intestinal surgery in one subject).

The majority of the non-serious AEs (NSAE) were related to mild infections or gastrointestinal disease, abnormal immunology tests (antibodies of indeterminate specificity in assays for FIX or rFurin), or arthralgia, a well-described complication of hemophilia, and not related to RIXUBIS. There does not appear to be an age-dependency or relationship to race in the incidence of AEs andSAEs.
Ten AEs in 8 (8.1%) unique subjects were considered serious.

None of the SAEs were considered related to RIXUBIS or to a commercial rFIX used as a comparator in the PK cross-over portion of the pivotal study. There were no deaths.

AEs related to treatment:
The only AEs rated as related to RIXUBIS by the investigator or the sponsor were 6 non-serious AEs in 5 (5.1%) subjects. Two subjects were reported to have a positive (and transient) rFurin antibody test result (1:80), one subject experienced an AE of hemorrhagic anemia, and one subject experienced two AEs of dysgeusia. Of these 6 AEs, 3 were rated as mild, 2 as moderate and 1 AE was of unknown severity and causality (pain in extremity).

Immunogenicity:
No subjects have developed inhibitory antibodies to FIX with a titer ≥ 0.6 BU or treatment-related positive binding antibodies to FIX and CHO proteins throughout the RIXUBIS clinical development program thus far.

Thrombogenicity:
No thrombotic events occurred in any subject in the integrated analysis of safety.

Hypersensitivity:
No severe allergic reactions were reported for any subject in the integrated analysis of safety.

7.2 Critical Review of Available Data

Hemophilia B represents a rare X-linked genetic disorder of primary hemostasis, caused by coagulation factor IX (hemophilia B). Hemophilia B affects 1-2 infants per 50,000 male newborns [4]. Individuals with severe deficiency require life-long coagulation factor replacement therapy, for treatment or prevention of spontaneous or traumatic bleeds. 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 [5;6]. 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.[5;7;8.] 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 [5]. Immune tolerance induction (ITI) is frequently less successful in these patients and subjects often develop a nephrotic syndrome as a result of ITI [5].

Pharmacokinetics, safety and efficacy has been shown in a phase I/III clinical study in previously treated patients (PTPs) with severe (<1% FIX) and moderately severe (≤ 2 % FIX level).[1;3] RIXUBIS was safe and well tolerated in all 73 patients in the full analysis set. AEs considered related to treatment (2.7% incidence) were mild and transient. No hypersensitivity reaction, inhibitor formation or thrombotic events were observed. PK equivalence of RIXUBIS in comparison to an already licenced recombinant FIX was evaluated by comparing the ratio of the geometric mean of the area under the curve (AUC) per dose over the 0-72h period. Twice weekly prophylaxis (mean 49.5 IU/kg/dose) was effective in preventing bleeding episodes with a significantly lower (by 79%) annualized bleeding rate (ABR) compared to a historical group treated on-demand (4.2 Vs 20.0). Of the subjects on prophylaxis, 43% (24/56) did not bleed throughout the duration of the study. Of 249 acute bleeds, 211 (84.7%) were controlled with 1 or 2 infusions of RIXUBIS. Hemostatic effectiveness was rated excellent or good in 96% of all treated bleeding episodes. The results of this study indicate that RIXUBIS treatment is safe and efficacious in treating bleeds and as routine prophylaxis in patients aged 12 years and older with hemophilia B [2;3].

Additionally, this clinical trial assessed aspects of quality of life (QoL) of hemophilia B patients [2]. Health-related QoL (HRQoL) burden of hemophilia B, the benefit of RIXUBIS prophylaxis and the HRQoL benefits of achieving a zero annual bleed rate was investigated. Short-Form Health Survey (SF-36) scores showed statistically significant and clinically meaningful improvements in overall physical HRQoL measured by the Physical Component Summary (PCS) score, Bodily Pain (BP) and Role Physical (RP) domains. Subjects that switched to prophylaxis from intermittent prophylaxis or on-demand treatment experienced more pronounced improvements not only in PCS, BP and RP scores, but also in Vitality (VT), Social Functioning (SF) and General Health (GH) domains. Subjects achieving zero bleeds reported reduced BP scores. Therefore prophylaxis with RIXUBIS improved HRQoL in patients with moderately severe and severe hemophilia B by reducing bleeds.

RIXUBIS was investigated for prophylactic use in pediatric PTPs aged <12 years with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) hemophilia B. The purpose of this prospective clinical trial was to assess the safety, hemostatic efficacy, and PK profile of RIXUBIS which was administered as prophylaxis twice a week over 6 months, and on-demand for treatment of bleeds. Safety was assessed by the occurrence of related AEs, thrombotic events and immunologic assessments. Efficacy was evaluated by ABR, and by treatment response rating (excellent, good, fair, none). PK was assessed over 72 hours.

None of the 23 treated subjects experienced an SAE or AE related to treatment. There were no thrombotic events, and no inhibitory or specific binding antibodies against FIX, rFurin or CHO protein. Twenty-six bleeds (19 non-joint vs. 7 joint bleeds) occurred, of which 23 were injury-related (mean ABR 2.7 ±3.14, median 2.0). Twenty subjects (87%) did not experience any bleeds of spontaneous etiology. Hemostatic efficacy of RIXUBIS was excellent or good for >96% of bleeds (100% of minor, 88.9% of moderate, and 100% of major bleeds); the majority (88.5%) resolved after 1-2 infusions. The PK analysis revealed that the incremental recovery (IR) 30 minutes after infusion was consistent over time. IR was associated with age, increasing IR was observed with increasing age (mean IR of all subjects (n=23): 0.665 ±0.1632 (median 0.685); subjects <6 years (n=11): mean IR 0.586±0.1320 (median 0.591); and in subjects between 6 and 12 years mean IR was 0.731±0.1615 (median 0.714). Longer $T_{1/2}$ and lower IR were observed in younger children (<6 years) compared to the older age group. In summary, RIXUBIS was efficacious in preventing and controlling bleeds, and was safe in pediatric patients aged <12 years with hemophilia B [9;10;11].

The efficacy and safety of RIXUBIS was further investigated in a prospective, open-label, uncontrolled, multicenter phase III study in PTPs with severe or moderately severe hemophilia B undergoing surgical or other invasive procedures [2;3]. In 40 subjects, aged 12-65 years old undergoing surgical, dental or other invasive procedures, hemostasis was rated ‘excellent’ intraoperatively and also postoperatively in subjects without a drain. In surgeries where drain was employed, the hemostasis rating at the time of drain removal were either “excellent” or “good”. Surgical studies are of particular importance as they usually document the use of very high doses of recombinant replacement factor products which can result in safety concerns [12]. This surgical study shows that RIXUBIS was safe and well tolerated in subjects who were treated for peri-operative management. No bleeding complications were observed during intra- or postoperative period. Only one possibly related AE (hemorrhagic anemia) was reported; this event was resolved by the time of study completion. No severe allergic reactions were reported. No thrombotic events or inhibitor formation was observed. Thrombosis has been reported following use of plasma derived or rFIX replacement by continuous infusion [13;14;15]. Neither the surgical study for RIXUBIS nor the phase I/III safety and efficacy study showed any indication for thrombotic events [2].

Findings From Nonclinical Studies

The nonclinical program for RIXUBIS evaluated thepharmacodynamics (PD) , PK, safety, efficacy and immunogenicity of RIXUBISin different animal species [16]. RIXUBIS was efficacious in all three pharmacodynamic models. PK was dose related. PK results showed that rFIX activity and rFIX antigen concentration declined in a biphasic manner, similar to a previously licenced rFIX. RIXUBIS was well tolerated in rabbits and macaques at all dose levels, no thrombogenic events, and no adverse clinical, respiratory or cardiovascular effects occurred. RIXUBIS had a comparable immunogenicity profile in mice to an previously licenced comparator rFIX. Thus RIXUBIS has a favourable nonclinical safety and efficacy profile, predictive of a comparable effect to that of a previously licenced rFIX in humans [16].

8. RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

The study aims to assess hemostatic effectiveness and safety in routine clinical practice with a new rFIX product (RIXUBIS) using any therapeutic regimen administered to hemophilia B patients .
This post-authorization multicenter cohort study is designed to measure short and long-term objectives in terms of effectiveness, safety, joint health, quality of life and economic outcomes.

8.2 Primary Objective

The primary objective of the study is to assess hemostatic effectiveness in the prevention of bleeding events in subjects with hemophilia B receiving rFIX (RIXUBIS) according to any therapeutic regimen in routine clinical practice.

8.3 Secondary Objectives

- To describe hemostatic effectiveness in the treatment of bleeding events in subjects with hemophilia B receiving rFIX (RIXUBIS).
- To describe the safety and immunogenicity in subjects with hemophilia B receiving rFIX (RIXUBIS).
- To describe joint health outcomes in subjects receiving rFIX (RIXUBIS).
- Health-Related Quality of Life (HR-QoL) objectives:
  - To describe HRQoLin subjects receiving rFIX (RIXUBIS)
  - To describe acute and chronic pain associated with hemophilia in subjects receiving rFIX (RIXUBIS)
  - To describe the physical activity in subjects receiving rFIX (RIXUBIS)
- To describe hemophilia-related co-morbidity in subjects receiving rFIX (RIXUBIS)
- To describe healthcare resources use in subjects receiving rFIX (RIXUBIS) on-demand or prophylactically.

9. RESEARCH METHODS

9.1 Study Design

This study is a post-authorization, prospective, uncontrolled, non-interventional, multicenter cohort study Approximately 80 subjects with congenital hemophilia B will be enrolled. Subjects must be prescribed rFIX (RIXUBIS) by the treating physician before study participation. Data will be collected over a period of 4 years from the time of study enrollment. The treating physician will determine the treatment regimen, as well as the frequency of laboratory, radiological, and clinical assessment according to her/his routine. Data will be collected on routinely scheduled and emergency visits. There is no binding visit schedule, however it is recommended that the subjects have at least annual visits. Available data from these visits shall be transcribed onto the electronic case report forms (e-CRFs).

It is considered standard practice for subjects with hemophilia to maintain a diary either on paper or in an electronic form (e.g. Smart Medication) which captures FIX treatment and disease related data. A subject diary will be provided to each subject to assist with the standardization of data collection as stated in Section 9.4.2. Nevertheless, the completion of the diary is a voluntary effort by the individual subject or subject's legally authorized representative. All bleeding events and their treatment recorded in subject diaries during study participation period will be transcribed onto e-CRFs.

QoL questionnaires will be provided at baseline and on an annual basis to subjects or their legally authorized representatives.

As no hypothesis testing or interval estimation will be applied, the sample size for the study is not based on statistical considerations.

9.1.1 Primary Endpoint

See also Section 9.3.1.

Preventive Effectiveness

To describe hemostatic effectiveness in the prevention of bleeding events in subjects with hemophilia B receiving rFIX (RIXUBIS) in routine clinical practice

9.1.2 Secondary Endpoints

See also Section 9.3.2

9.1.2.1 On-demand treatment

To describe hemostatic effectiveness in the treatment of bleeding events in subjects with hemophilia B receiving rFIX (RIXUBIS). For details, see Section 9.3.2.1.

9.1.2.2 Safety and Immunogenicity

Safety and immunogenicity in subjects receiving rFIX (RIXUBIS) using any therapeutic regimen in routine clinical practice. For details, see Section 9.3.2.2.

9.1.2.3 Joint Health/Function Outcomes

To describe joint health outcomes in subjects receiving rFIX (RIXUBIS) in routine clinical practice setting, using any therapeutic regimen. For details, see Section 9.3.2.3.

- **Joint health** will be assessed by either physical examination including muscoskeletal evaluation (using the Hemophilia Joint Health Score [HJHS]) and the assessment of pressure points, or by imaging techniques such as radiographs (Petterson scale) and/or magnetic resonance imaging (MRI) (scoring system developed in Lund).

9.1.2.4 Health-related Quality of Life

- To describe health-related quality of life (HRQoL) in subjects receiving rFIX (RIXUBIS) (Section 9.3.2.4.1).
- To describe acute and chronic pain associated with hemophilia in subjects receiving rFIX (RIXUBIS) (Section 9.3.2.4.2).
- To describe the physical activity in subjects receiving rFIX (RIXUBIS) (Section 9.3.2.4.3).

9.1.2.5 Haemophilia-related comorbidity

To describe hemophilia-related comorbidity in subjects receiving rFIX (RIXUBIS) (Section 9.3.2.4.4).

9.1.2.6 Healthcare resource use

To describe healthcare resource use in subjects receiving rFIX (RIXUBIS) (Section 9.3.2.4.5).

9.2 Setting

9.2.1 Medicinal Product

Treatment with RIXUBIS will be performed as specified in the product label and will be guided by clinical experience.

Administration, packaging, labeling, and storage for the product are described in the product label.

The investigator will record the treatment regimen, dose and dosing frequency, in the e-CRF.

9.2.2 Duration of Study Period(s) and Subject Participation

The overall duration of the study is expected to be 7 years from study initiation (i.e. first subject enrolled) to study completion. The recruitment period is planned to be approximately 3 years. The subject participation period for each individual subject is planned to be 4 years from enrollment to study completion (i.e. last study visit) unless prematurely discontinued.

9.2.3 Subject Selection Criteria

9.2.3.1 Inclusion Criteria

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

1. Subject has congenital hemophilia B (FIX level ≤5%)
2. Subject is prescribed rFIX (RIXUBIS) by the treating physician as part of routine clinical practice
3. Subject or subject's legally authorized representative provides informed consent.

9.2.3.2 Exclusion Criteria

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

- Known hypersensitivity or presence of any contraindication to rFIX
- Disseminated intravascular coagulation (DIC)
- Acute thrombosis or embolism (including myocardial infarction)
- Other severe concomitant clinically relevant conditions or bleeding disorders that in the investigator's opinion precludes the inclusion of the patient.

9.2.4 Informed Consent and Enrollment

Any patient who directly, or indirectly through a legally authorized representative, provides informed consent (ie, signs and dates the informed consent form (ICF) or assent form, if applicable) is considered to be enrolled in the study.

9.2.5 Subject Identification Code

The following series of numbers will comprise the subject identification code (SIC): protocol identifier (251401) to be provided by the MAH, 3-digit study site number (eg, 002) and 3-digit subject number (eg, 003) reflecting the order of enrollment (ie, signing the informed consent form). For example, the third subject who signed an informed consent form at study site 002 will be identified as Subject 251401-002-003. All study documents (eg, e-CRFs, clinical documentation, etc.) will be identified with the SIC. Alternative uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject, in compliance with laws governing data privacy.

9.2.6 Screening and Follow-up

The study site is responsible for maintaining an enrollment log that includes all subjects enrolled. Data on recruited subjects are expected to be collected during the routine visits. The data will be prospectively collected at the sites and recorded onto e-CRFs from hospital medical records - the subject diaries will be completed by the subjects at home. Details on the assessments/data to be recorded for screening and follow-up, can be found in Table 2.

Table 1
Schedule of Study Procedures and Assessments[a]

Procedures / Assessments	Screening Visit	Interim Visits[e]	Annual Visits	Termination Visit
Informed Consent[b]	X			
Eligibility Criteria	X			
Medical History including Hemophilia treatment history	X			
Rixubis Treatment Regimen	X	X	X	X
Non-drug Therapies	X	X	X	X
Concomitant Medications	X	X	X	X
Physical Examination	X	X	X	X
Vital Signs	X	X	X	X
Joint Evaluation	X	X	X	X
Chronic Pain Assessment	X	X	X	X
Surgical Procedures		X	X	X
Subject Diary	D	R/D	R/D	R
Adverse Events[c]		X	X	X
Hemostatic Effectiveness		X	X	X
Health Resource Use	X	X	X	X
HRQoL Questionnaires	X		X	X
Acute Pain Assessment[d]		X	X	X
Daily Activity Level	X		X	X
End of Study Form				X

[a] Standard procedure according to routine clinical practice
[b] Occurs at enrollment
[c] AEs will be collected whenever they occur. Each AE will be evaluated by the investigator for seriousness (Section 11.1.1.1), severity (Section 11.1.2.1) and causal relationship (Section 11.1.2.2)
[d] As part of the diary
[e] As needed

Table 2
Clinical Laboratory Assessments

Procedures / Assessments	Screening Visit	Interim Visits[b]	Annual Visits	Termination Visit
Inhibitor to FIX [a]	X	X	X	X
FIX clotting assay[a]	X	X	X	X

[a] Standard procedure according to routine clinical practice
[b] As needed

The following data will be collected at the screening visit according to routine clinical practice:

- Year of birth
- Gender
- Height
- Weight
- If a pediatric patient: percentile of height growth curve and weight growth curve
- Pulse rate
- Blood pressure
- Medical history
- History of hypertension
- Baseline FIX levels
- Family history of inhibitors.
- History of inhibitor development
  - Date(s) of inhibitor detection
  - Total FIX EDs at time of inhibitor detection
    Where the exact numbers of ED is not available, one of the following ranges should be selected: 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.
- Current RIXUBIS treatment
  - Dosage and dosing intervals
  - Regimen start date

  - Total EDs to RIXUBIS at screening visit
    Where exact numbers 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.

- FIX product used prior to RIXUBIS treatment initiation (maximal retrospective time-period of 12 months before treatment initiation)
  - Name of product, dosage and dosing interval
  - Regimen start and end date
  - Total EDs to FIX products at screening visit
    Where exact numbers 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.
- Sporting activities (type and frequency)
- Ambulatory status, including need for ambulatory assistance devices such as leg braces, cane, crutches, or wheelchair
- Number of bleeding episodes (ABR and annualized joint bleeding rate (ABJR)) categorized by severity within the last 12 months.
- Status of joint health as assessed by physical exam at study enrollment
  + Musculoskeletal evaluation of target joints using HJHS within the last 5 years prior to study enrollment.
- Status of joint health assessed by imaging techniques (e.g. MRI or X-ray)
  +radiological evaluation of any joints using the Petterson score within the last 5 years prior to study enrollment.

The following data, if available will be collected at interval and termination visits:

- Total EDs to RIXUBIS since the last visit
- Current RIXUBIS treatment regime (if changed):
  - Dosage and dosing intervals
  - Regimen change date
- Height, Body weight
- FIX inhibitor titer
- Bleed occurrence, including location, etiology, and severity

- Status of joint health as assessed by physical exam
  + Musculoskeletal evaluation of target joints using the HJHS.
- Status of joint health as assessed by imaging techniques (e.g. MRI, X-ray)
  + Radiological evaluation of any joints using the Pettersson score.
- HRQOL measures, surgical data and activity levels (including sporting activities)

9.2.7 Subject Withdrawal and Discontinuation

Subjects 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. The data collected on withdrawn subjects will be used in the analysis up to the date of withdrawal and included in the study report.

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). Additionally, the investigator may decide to discontinue any subject from the study.

9.2.8 Study Stopping Rules

Stopping rules will not be established for this study.

9.3 Variables

9.3.1 Variables for assessing the primary endpoint

9.3.1.1 Effectiveness of prophylaxis

- Effectiveness as measured by
  - Overall effectiveness assessment for the prevention of bleeding
  - ABR and monthly bleeding rate (MBR), all bleeds
  - AJBR, monthly joint bleeding rate, all joint bleeding events
  - ABR, MBR, trauma related
  - Overall effectiveness assessment for prophylaxis with an “excellent-to-poor” 4-point scale, as rated by the patients or care-giver (for details, see Appendix 1, Table 4).

9.3.2 Variables for assessing the secondary endpoints

9.3.2.1 Effectiveness of on-demand treatment

(see APPENDIX 1)

- Overall effectiveness assessment for on-demand treatment with an "excellent-to-poor" 4-point scale, as rated by the patients or care-giver, also a rating of the severity of bleeding (mild, moderate, severe) (for details, see Appendix 1, Table 3)
- Total weight-adjusted dose required for bleeding episode resolution
- Number of rFIX (RIXUBIS) infusions required for bleeding episode resolution.
- For perioperative treatment:
  - Type and severity of the surgical intervention
  - Intraoperative and postoperative effectiveness according to an "excellent-to-poor" 4-point scale (surgery) assessed by the physicians
  - Total weight-adjusted dose and number of infusions of rFIX (RXUBIS) required to cover the surgical procedure
  - Number of days spent in hospital related to the surgery
  - Need for supplemental hemostatic therapy (i.e. tranexamic acid, etc.).

9.3.2.2 Safety and Immunogenicity

- Incidence of inhibitors in PTPs with history of inhibitors and with FIX <1%, ≤2% and >2-5%
- Incidence of inhibitors in PTPs without history of inhibitors and with FIX <1%, ≤2% and >2-5%
- Incidence of inhibitors in previously untreated patients (PUPs) with FIX <1% and ≤2% and >2-5%
- Treatment regime after an inhibitor has occurred in PUPs and PTPs
- Incidence and severity of SAE and NSAE
- Incidence and severity of therapy-related SAE and NSAE
- Incidence of life-threatening bleeding episodes
- Incidence of thromboembolic events.

9.3.2.3 Joint Health/Function Outcomes

(see APPENDIX 2)

The health status of the joints (e.g. knee, ankles, elbows) will be further assessed by the following endpoints, where available

- HJHS [17]
- Radiographs, using the Pettersson scale [18]
- Magnetic resonance imaging scoring system
- Total number of target joints [19]
- Number of invasive surgical procedures, such as (not exclusively orthopedic) surgery, radiosynovectomy, and chemosynovectomy per year per patient
- Incidence of new target joints

A target joint is defined as a joint in which at least 3 or more spontaneous bleeds into a single joint within a consecutive 6 month period. Where there have been ≤ 2 bleeds into the joint within a consecutive 12 month period the joint is no longer considered a target joint [19].

9.3.2.4 Health-Related Quality of Life Variables

9.3.2.4.1 Health-Related Quality of Life Questionnaires (HRQoL Questionnaires)

- HRQoL questionnaires in subjects receiving rFIX (RIXUBIS) will be provided at the screening visit and on an annual basis to subjects or their legally authorized representatives. QoLquestionnaires may not be available in all languages and therefore will not be available at all study sites.
- SF-12 version 2.0 (SF-12v2), and EQ-5D questionnaires – for adult subjects ≥ 18 years
  - The SF-12v2 is a self-administered generic measure of HRQoL derived from the SF-36. It covers the same 8 health domains as the SF-36v2 with one or two questions per domain, and yields 8 domain sores as well as two Physical and Mental Component Summary measures, referred to as PCS-12 and MCS-12. The recall period is the past 4 weeks. A higher score indicates better QoL.
  - The EQ-5D is a generic instrument developed by the EuroQoL group to assess subject's health status for clinical and economic appraisal. The EQ-5D is a self-administered instrument comprosed of two parts. The first part is a descriptive system consisting of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels of severity: no problems, some problems, extreme problems.

Responses to the five dimensions are combined and converted into a single preference-based health utility index by applying value sets. The second part is a 20-cm vertical visual analog scale (EQ-VAS) to rate one's current HRQoL, anchored at 0 and 100 for worst and best imaginable health states, respectively. For either part, the recall period is the present time. A higher score indicates better QoL.

- SF-10, is a generic measure of functional health and well-being for children aged 5-18 and is parent-completed. The SF-10v2 contains ten items adapted from the Child Health Questionnaire that estimate scores for a Physical (PHS) and a Psychosocial (PSS) Summary Measures. The recall period is the past 4 weeks. A higher score indicates better QoL.
- EQ-5D-Y (Youth version). is a generic measure of health status designed for children aged 7-12, and is completed by the parent or legal guardian. Descriptive system of youth health-related quality of life states consisting of five dimensions (mobility, looking after myself, doing usual activities, having pain or discomfort, feeling worried, sad or unhappy) each of which can take one of three responses. The responses record three levels of severity ("no problem," "some or moderate problems," "extreme problems/impossible to do") within a particular EQ-5D-Y dimension. The recall period is the present time. A higher score indicates better QoL.
- HaemoQoL scale for both adults (Haem-A-QoL > 18 years) and children (HaemoQol) aged 4-17. Patients are to fill out the questionnaire version for their child's age at the current annual visit.
  - The Haemo-QoL is a disease-specific HRQoL assessment instrument for children and adolescents with hemophilia. There are 3 sets of psychometrically tested questionnaire versions of variable length for three age groups of children, as well as their parents/ legally authorized representative. In addition to the full version, a short version for small children (4-7 years) containing 16 items and a short version for older children (8-16 years) containing 35 items have been developed. An 8-item index version was developed spanning all age groups which is also available for completion by the pediatric patient or their parent/ legally authorized representative. The questionnaires yield domain scores and a total score. A higher score indicates greater impairment.
  - The Haem-A-QoL is a disease-specific HRQoL assessment instrument designed for adult patients with hemophilia. It consists of 46 items pertaining to 10 dimensions (physical health, feelings, view of yourself, sport and leisure, work and school, dealing with hemophilia, treatment, future, family planning, partnership and sexuality). It yields domain scores and a total score. A higher score indicates greater impairment.

9.3.2.4.2 Acute and Chronic Pain

Acute and chronic pain in subjects receiving rFIX (RIXUBIS) will be assessed.

- Acute pain associated with hemophilia, as measured by individual bleeding episodes, using the Numeric Rating Scale (NRS) or Pediatric "Wong Baker Face Scale" as appropriate
- Chronic pain [defined as "Continuous and/or intermittent pain, related to the pathophysiology of hemophilia, requiring intervention (pharmacological or non-pharmacological pain treatment), in which the cause of pain cannot be readily removed, occurring more than once a week and lasting 3 months or more"] associated with hemophilia [20], if available, assessed by the Numeric Rating Scale (NRS) or Pediatric "Wong Baker Face Scale" as appropriate.
- Numeric Rating Scale
  The numeric rating scale (NRS) is a unidimensional measure of pain intensity in adults. The most commonly iteration used is the 11 item NRS. The common format is a horizontal bar or line. Similar to the pain Visual Analog Scale (VAS), the NRS is anchored by describing pain severity extremes. It can be administered either verbally or graphically for self-completion and the subject is asked to indicate the numeric value on the segmented scale that best describes pain intensity.
- Pediatric subjects or subjects who have difficulty quantifying their pain numerically can be asked to assess the pain by using the following Wong Baker Face Scale.

Explain to the individual that each face is for an individual who feels happy because he has no pain (hurt) or sad because he has some or a lot of pain. Face 0 is very happy because he does not hurt at all. Face 1 hurts just a little bit. Face 2 hurts a little more. Face 3 hurts even more. Face 4 hurts a whole lot. Face 5 hurts as much as you can imagine, although the individual does not have to be crying to feel this bad. Ask the individual to choose the face that best describes how he is feeling. This rating scale is recommended for individuals 3 years and older. Brief instructions: point to each face using the words to describe the pain intensity. Ask the individual to choose the face that best describes the pain and record the appropriate number.

During the screening and on an annual basis – or more frequently based on the standard practice at the site - the investigators shall ask subjects to rate the average level of chronic pain associated with hemophilia over the period of 4 weeks prior to visit date using the NRS or Pediatric "Wong Baker Face Scale" as appropriate. The scores will be recorded in the subject diary on a voluntary basis.

9.3.2.4.3 Physical Activity Level

- Daily activity level, if available, will be assessed by the Hemophilia Activity Level scale (HAL) [21;22] in adults and Pediatric Hemophilia Activity Level scale (PedHAL) in children. The HAL measures activities involving the upper extremities, basic activities involving the lower extremities, and complex activities involving the lower extremities, as well as an overall physical activity score for adults. The aim of this questionnaire is to determine the ability of the subject to perform the listed activities:
  - Lying down/ sitting / kneeling / standing
  - Functions of the legs
  - Functions of the arms
  - Use of transportation
  - Self-care
  - Household tasks
  - Leisure activities and sports
  - Adaptations and using an aid.

  There are six different response options (impossible, always, mostly, sometimes, rarely, never) for each type of activity. For activities, the recall period is the past month. The HAL yields 7 domain scores and an overall score. A higher score represents more functional limitations.
- The pedHAL measures a number of activities involving the upper extremities, basic activities involving the lower extremities, and complex activities involving the lower extremities, as well as an overall physical activity score for children. The aim of this questionnaire is to determine the ability of children to perform the listed activities:
  - Lying down/ sitting / kneeling / standing
  - Functions of the legs
  - Functions of the arms
  - Use of transportation
  - Self-care
  - Household tasks
  - Leisure activities and sports
  - Adaptations and using an aid.

Parent/proxy (age 4-8) and child (8-18) versions are available. There are six different response options (impossible, always, mostly, sometimes, rarely, never) for each type of activity. For activities, the recall period is the past month. The pedHAL yields 7 domain scores and an overall score. A higher score represents more functional limitations.

9.3.2.4.4 Haemophilia-related comorbidities

The following will be recorded:

- Incidence of target joint intervention, including surgery, radiosynvectomy and chemosynvectomy.
- Incidence of pseudotumor development.

9.3.2.4.5 Healthcare resource use

Healthcare resource use in subjects receiving rFIX (RIXUBIS) will be assessed to estimate health-related direct and indirect costs if applicable in the country. Also, additional resources which are available at the hemophilia treatment center and routinely used by the subject will be assessed. Direct medical costs, direct non-medical costs and indirect costs (if applicable and available) will be appraised by the valuation of the following resources:

- number of home care nursing visits
- number of physiotherapy sessions
- number of orthopedic consultations
- number of nutrional guidance and training sport/school counseling sessions
- number of psychological support/counseling sessions
- number of social counseling sessions
- number of social support (e.g. disease communicator/trouble shooter) visits
- number of visits for emergency FIX stock available at center
- number of 24h hotline calls available at center
- number of phone counseling sessions of patients
- number of laboratory diagnostics visits available at center
- number of dental consultations
- number of infectiology (immunological counseling) sessions

- usage of an electronic diary/smart phone application (e.g. Smart Medication)
- financial help for center visits (travel expense reimbursement)
- number of patient education (e.g. injection training) sessions
- number of scheduled and unscheduled visits at the site
- number of ER visits
- number of inpatient hospitalization, length of stay and severity of complication related to hemophilia (excluding planned surgery)
- length of stay in the hospital per inpatient hospital and severity/kind of complication
- number of days the subject cannot follow normal daily routine (e.g. school, work) due to bleeding episodes or their treatment.

9.3.3 Medical History, Medications, and Non-Drug Therapies

At screening, the subject's medical and surgical history will be described for the following body systems: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary systems. Hemophilia history and treatment history will be captured, including start and end dates of past treatments where available.

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

9.3.4 Physical Examinations

At interval visits, a physical examination (see also Table 1) will be performed. At screening, if an abnormal condition is detected, the condition will be described on the medical history e-CRF. At subsequent study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE e-CRF. If the abnormal value was not deemed to be an AE because it was due to an error, due to a pre-existing disease (described in Section 11.1.1.4), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that must be specified, the investigator will record the justification on the source record.

9.3.5 Clinical Laboratory Parameters

The investigator's assessment of each laboratory value will be recorded on the eCRF. For each abnormal laboratory value, the investigator will determine whether the value is clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 11.1 , 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 preexisting disease (described in Section 11.1.1.4), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, ie because it is due to a preexisting disease, due to a lab error, or due to another issue that will be specified. However, 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.

9.3.6 Vital Signs

Vital signs will include height (cm) and weight (kg). Height and weight will be collected, if available, at screening visit, each annual interval visit, and study completion/termination. For pediatric patients, percent of growth and height curves will be collected. Vital signs will be recorded on the CRF. For abnormal vital signs, the investigator will determine whether or not to report an AE (see definition in Section 11.1 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.

9.3.7 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, completed the study according to the protocol.

Reasons for completion/discontinuation will be reported on the Completion/ Discontinuation CRF, including: completed, screen failure, discontinuation due to an AE, discontinuation by subject (eg, lost to follow-up, dropout), study terminated by the MAH, or other (reason to be specified by the investigator). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF and will be used in the analysis and included in the study report.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations performed as part of the evaluation of the event will be reported to the MAH. Details of the outcome may be reported to the appropriate regulatory authorities by the responsible party.

9.4 Data Sources

9.4.1 Source Data

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 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, questionnaires, subject diaries or evaluation checklists, outcomes reported by subjects, 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 study.

For additional information on study documentation and CRFs see Section 9.6.1. The use of subject diaries is described in Section 9.4.2.

Data will be prospectively collected at the centers and recorded onto e-CRFs from hospital medical records and the subject diaries (paper or electronic) documented by the patient (see Section 9.4.2).

9.4.2 Subject Diary

It is considered standard practice for subjects with hemophilia to maintain a diary which captures treatments and disease-related data.

Both paper and electronic subject diaries will used in this study. Diaries will be offered to each subject at the screening visit and at annual visits to record the following information:

- Number of RIXUBIS units required for bleed resolution
- Number of RIXUBIS infusions required for bleed resolution
- Bleeding episodes
- Effectiveness assessment for the treatment of each bleed

- Number of days in which subjects cannot follow normal daily routine (e. g. school, work) due to bleeding episodes or their treatment
- Acute pain assessment using Numeric Rating Scale (NRS) or Pediatric Wong Baker Face Scale

Completion of the subject diary is a voluntary effort by the individual subject or subject's legally authorized representative. If used, the diary will remain with the subject for the duration of the study. Untoward events recorded in the diary will be reported as AEs according to the investigator's discretion and clinical judgment.

Subject entries in the diaries will serve as source records. In the case of eDiaries, the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the eDiary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the CRF by a validated transfer.

In the case of paper diaries, 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.

9.5 Study Size

As no hypothesis testing or interval estimation will be applied, the sample size for the study is not based on statistical considerations. The sample size of approximately 80 evaluable subjects was selected as a reasonable number for a non-interventional study to recruit over the enrolment period planned for the study.

9.6 Data Management

9.6.1 Data Collection Methods

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 9.4.1) records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/MAH, enrollment and screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), subject diaries (if used), and data clarifications requested by the MAH.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper source 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 and all data should be entered within 5 days of becoming available.

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) version of the complete set of CRFs for each subject will remain in the investigator file at the study site.

The handling of data by the MAH, including data quality assurance, will comply with regulatory guidelines and the standard operating procedures of the MAH. Data management and control processes specific to the study will be described in the data management plan (see Section 14.1).

9.6.2 Laboratory and Reader Standardization

No central laboratories will be used, and no inter-laboratory standardization methods and reader standardization methods for laboratory tests will be carried out. Each local laboratory will provide normal value ranges.

9.6.3 Software

All data processing, summarization and analyses will be performed with the SAS®, using the most current accessible version of SAS software.

9.7 Data Analysis

9.7.1 Datasets and Analysis Cohorts

The effectiveness analysis will be carried out on the primary and secondary endpoints of the study for the following treatment regimens:

- Standard prophylaxis
- On-demand treatment
- Episodic prophylaxis
- ITI

Effectiveness of switch from on-demand to prophylaxis dataset (ESODTP)

Evaluation of effectiveness (ABR, AJBR) after switch from on-demand regimen to prophylaxis in moderate moderately severe and severe hemophilia B patients.

Safety Analysis Set (SAS)

The SAS will consist of data for all subjects who were enrolled, met all inclusion and none of the exclusion criteria, and received at least 1 infusion of FIX (RIXUBIS). If 2 or more AEs are reported together as a unit, the individual Medical Dictionary for Regulatory Activities (MedDRA) preferred terms will be counted as separate events.

Effectiveness Full Analysis Set (EFAS)

The EFAS will consist of data from all subjects who were enrolled, met all inclusion and none of the exclusion criteria. This dataset will be used for the primary effectiveness analysis for the comparison of annualized bleeding rates (ABR, AJBR) between each independent treatment regimen (i.e., prophylaxis, on-demand).

Calculation of Annualized Bleeding Rates (ABR) and monthly Bleeding Rate (MBR)

The ABR will be calculated as follows: (total number of bleeding episodes÷observed treatment period in days) * 365.25. The monthly bleeding rates (MBR) will be calculated as follows: (total number of bleeding episodes÷observed treatment period in days) * 30.5. The treatment period for surgeries will be excluded from the bleed rate calculation.

Bleeding occurring prior to the first prophylactic infusion will not be included in the estimation of bleeding rate. The observation period for the on-demand regimen will commence on the day of enrollment (met all inclusion and none of the exclusion criteria); the period for prophylaxis will commence at the first prophylactic infusion once enrolled (met all inclusion and none of the exclusion criteria).

Minimal Observed Treatment Period to Estimate ABR

For enrolled subjects that have met all inclusion and none of the exclusion criteria, subjects who have at least 1 assessment [defined as having a minimum of 3-month (≥90 days) observational period on regimen] but do not complete the full study period of four years, the ABR will be estimated from the interval assessments. For subjects who do not have at least 1 interval assessment, the median rate observed for the assigned regimen will be substituted.

Health Related Quality of Life Analysis Set (HRQoLAS)

The HRQoLAS will consist of all subjects who have been enrolled and met all inclusion and none of the exclusion criteria and who have provided any available assessments at any available study visit.

Pharmacoeconomics Analysis Set (PEAS)

The PEAS will consist of all the subjects that have been enrolled, met all inclusion and none of the exclusion criteria and have provided any available assessments at any available study visit.

Joint Health/Function Analysis Set (JHFAS)

The JHFAS will consist of all subjects who have been enrolled, met all inclusion and none of the exclusion criteria and have provided any available assessments at any available study visit.

9.7.2 Handling of Missing, Unused, and Spurious Data

If a subject's current weight is missing, the subject's last recorded weight will be used to calculate the weight-adjusted dose (IU/kg).

9.7.3 Methods of Analysis

Descriptive statistics of all endpoints will include specifically but not exclusively, arithmetic mean, medians, standard deviations, minimum, maximum, proportions, frequency counts, 25th and 75th percentiles, 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.

9.7.3.1 Primary Endpoint

(See Section 9.3.1)
To describe hemostatic effectiveness in the prevention of bleeding events in subjects with hemophilia B receiving rFIX (RIXUBIS) in routine clinical practice.

9.7.3.2 Methods of Analysis for Effectiveness Endpoints

The method of analysis will be applied to the effectiveness endpoint. The primary endpoint, ABR of all types of bleeding episodes, will be calculated for each subject and described for prophylaxis.

In addition, separate description of ABR will be provided for each of the following treatment regimens, assuming a minimum observed period of (≥90 days)is fulfilled:

- Standard prophylaxis
- On-demand treatment
- Episodic prophylaxis
- ITI

9.7.3.3 Methods of Analysis for Effectiveness Criteria

The annualized rate of bleeding episodes in joints, target joints, and other anatomical locations for the two independent samples (on-demand or prophylaxis) will be summarized. The frequency distribution for the number of infusions for bleed treatment will be reported for each of the on-demand and prophylaxis treatment regimens. The median number of infusions per bleeding episode for each subject will be calculated and the median for subjects in each treatment regimen will be compared using the Mann-Whitney (Wilcoxon-Rank Sum) test. The total weight-adjusted dose (IU/kg) per bleeding episode per subject will be described for both the on-demand and prophylaxis treatment regimens and will be compared using the Mann-Whitney (Wilcoxon-Rank Sum) test.

Corresponding to all treated FIX (RIXUBIS) bleeding episodes, the following parameters will be computed separately by treatment regimen (prophylaxis, on-demand):

Total number of subjects infused
Total bleed exposure days
Total number of bleed treatment infusions
Units administered per subject, per infusion (IU)
Units administered per subject, per bleed (IU)
Annualized units administered for bleed treatment, per subject (IU)
Total units administered for bleed treatment, per subject (IU)
Weight-adjusted dose per subject, per bleed (IU/kg)
Weight-adjusted dose per subject, per infusion (IU/kg)
Annualized weight-adjusted dose for bleed treatment, per subject (IU/kg)
Total weight-adjusted dose for bleed treatment, per subject (IU/kg)

Assessment of effectiveness:

Corresponding to subjects given prophylactic infusions (RIXUBIS) in this study, the following parameters will be computed by treatment regimen (prophylaxis, on-demand):

Total number of subjects infused
Total exposure days
Total number of infusions
Number of unique lots used
Units administered per subject, per infusion (IU)
Units administered per subject, per week (IU)
Units administered per subject, per month (IU)
Annualized units administered, per subject (IU)
Total units administered, per subject (IU)
Weight-adjusted dose per subject, per infusion (IU/kg)
Weight-adjusted dose per subject, per week (IU/kg)
Weight-adjusted dose per subject, per month (IU/kg)
Annualized weight-adjusted dose, per subject (IU/kg)
Total weight-adjusted dose, per subject (IU/kg)

The occurrence of new target joints and bleeding episodes used to assess new target joints will be summarized by treatment regimen.

9.7.3.4 Secondary Endpoints

(See Section 9.3.2)

9.7.3.4.1 Assessment of hemostatic effectiveness on-demand treatment

Total number (%) of treated bleeds and their corresponding hemostatic effectiveness ratings using an “excellent-to-poor” 4-point Likert scale as assessed by the subjects/ care-giver for treatments given at home, or by the investigator for treatments given in the hospital/clinic.

Separate ABRs will be provided for on-demand treatment, providing the minimum observed period is fulfilled (>90 days).

9.7.3.4.2 Methods of Analysis for Safety Endpoints

The analysis of AEs will be descriptive. All AEs will be categorized according to the MedDRA dictionary and summarized by system organ class and preferred term. AEs for which the investigator does not state the relationship to RIXUBIS administration will be included. All AEs will be cross-tabulated for relatedness, seriousness, and severity.

9.7.3.4.3 Joint Health/Function Outcomes

The methods of analysis for the secondaryeffectiveness endpoints (APPENDIX 2) are, if available:

- Physical exam using only the pain, bleeding, and physical exam parameters of the Hemophilia Joint Health Score (HJHS) score will be summarized for timepoints 0 (baseline), 12, 24, 36 and 48 months (termination visit) after study start (if available). Linear interpolation (for any time interval) and line extrapolation (for up to 0.5 years) will be used to derive an estimate of the score at these timepoints.
- MRI scoring will be summarized for timepoints 0 , 12, 24, 36 and 48 months (termination visit) after study start (if available). Linear interpolation (for any time interval) and line extrapolation (for up to 0.5 years) will be used to derive an estimate of the score at these timepoints.
- Radiographs using the Pettersson score will be summarized for timepoints 0, 12, 24, 36 and 48 months (termination visit) after study start (if available). Linear interpolation (for any time interval) and line extrapolation (for up to 0.5 years) will be used to derive an estimate of the score at these timepoints.
- Number of invasive surgical procedures, such as (not exclusively orthopedic) surgery, radiosynovectomy, and chemosynovectomy per year per subject.

9.7.3.4.4 Methods of Health Related Quality of Life (HRQoL) Endpoints Analysis

Below is the list of HRQoL assessments and other subjective measures:

- HRQoL questionnaires as measured in Section 9.3.2.4.1
- Acute pain associated with hemophilia, as measured with individual bleeding episodes, using the NRS or the Wong Baker Face Scale in pediatric subjects
- Chronic pain will be assessed based on current standard practice at the centre. Chronic pain, if any, will be assessed at the screening visit, on each annual visit and at the termination visit (as well as any interim visit) by using the NRS or the Wong Baker Face Scale in pediatric subjects
- Physical Activity as measured by the questionnaires detailed in Section 9.3.2.4.3.

HRQoL assessments, acute and chronic pain scales, and daily activity level will be summarized by treatment regimen (on-demand, prophylaxis) and by rater (subject or care-giver). If available, changes from baseline to follow-up study visit will be summarized by treatment regimen.

Of note, subjects may outgrow their initial version of the HaemoQoL questionnaire. In this case, changes from baseline will be assessed up to their move a further version of the questionnaire.

9.7.3.4.5 Methods of Health Resource Use Related (HRUR) Endpoints Analysis

All HRUR parameters will be summarized by treatment regimen (on-demand, prophylaxis). If available, changes from baseline to each follow-up study visit will be summarized by treatment regimen.

9.7.4 Planned Interim Analysis of the Study

Interim analyses and progress reports are planned every 12 months. Regular safety updates are to be scheduled as per the safety review plan.

9.8 Quality Control

9.8.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the competent/health authority and/or EC), and applicable regulatory requirements as described in the Non-interventional Trial Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the responsible party. 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.

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 Non-interventional Trial Agreement.

9.8.2 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 MAH or its representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Non-interventional Trial Agreement. If contacted by an applicable regulatory authority, the investigator will notify the MAH of contact, cooperate with the authority, provide the MAH with copies of all documents received from the authority, and allow the MAH to comment on any responses, as described in the Non-interventional Trial Agreement.

9.8.3 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol 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 MAH.

9.8.4 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, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Non-interventional Trial Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan (see Section 14.1).

9.8.5 Auditing

The MAH and/or MAH's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Non-interventional Trial Agreement. Auditing processes specific to the study will be described in the clinical quality management plan (see Section 14.1).

9.8.6 Non-Compliance with the Protocol

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the MAH may terminate the investigator's participation.

9.9 Limitations of the Research Methods

This cohort-based, non-interventional study aims to provide a real-life picture on the use of RIXUBIS in patients with congenital hemophilia B. On the other hand, this study design may reflect issues related to huge differences in treatment approach and dosing, laboratory monitoring and data recording. Nevertheless, findings will have a greater clinical relevance and lower selection bias than other study designs.

9.10 Other Aspects

None.

10. PROTECTION OF HUMAN SUBJECTS

10.1 Compliance Statement

This study will be conducted in accordance with this protocol and applicable national and local requirements for good pharmacovigilance practices.

10.2 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the Non-interventional Trial Agreement.

10.3 Ethics Committee(s) and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The 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 MAH's receipt of approval/favorable opinion from the EC and, if required, upon the MAH's notification of applicable regulatory authority(ies) approval.

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 relevant regulatory authorities, where applicable. The protocol amendment will only be implemented upon the MAH's receipt of approval and, if required, upon the MAH's notification of applicable regulatory authority(ies) approval.

10.4 Informed Consent

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

All patients/ and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable regulatory requirements. 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 MAH and approved by the EC and regulatory authority(ies), where applicable, (see Section 10.3). The informed consent form will include a comprehensive explanation of the study without any exculpatory statements, in accordance with the elements required by applicable 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 to the use of their data for the study, unless they withdraw voluntarily or are terminated from the study for any reason.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 Adverse Events

Each AE from the point of enrolment until study completion will be described on the AE e-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 definitions in Section 11.1.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 11.1.1.1
- Severity as defined in Section 11.1.2.1
- Causal relationship to medicinal product exposure as defined in Section 11.1.2.2

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and 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 e-CRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first.

11.1.1 Definitions

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 (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 a medicinal product, whether or not considered causally related to the medicinal product

11.1.1.1 Serious Adverse Event

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

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.

- Results in persistent or significant disability/incapacity (ie, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
  - Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)

For this study in particular, medically important events include:

- Thromboembolism/DIC/Fibrinolysis
- Reviewed and confirmed inhibitor development
- Nephrotic syndrome.

Uncomplicated pregnancies, following maternal or paternal exposure to product are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.

11.1.1.2 Non-Serious Adverse Event

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

11.1.1.3 Unexpected Adverse Events

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (eg, 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.

11.1.1.4 Preexisting Diseases

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.

11.1.2 Assessment of Adverse Events

For the purposes of this study, the following events experienced after enrollment will not be considered AEs, and thus, not included in the analysis of AEs:

- Bleeding events:
  will not be considered as AEs if they do not qualify as an SAE
- Elective surgeries:
  Elective and planned surgeries when these surgeries relate to a preexisting disease (see also 11.1.1.4) that has not worsened during study participation will not be considered as (S)AEs

Each AE from enrollment until study completion or withdrawal 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 definitions in Section 11.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 11.1.1.1
- Severity as defined in Section 11.1.2.1
- Causal relationship to medicinal product exposure as defined in Section 11.1.2.2.

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 study completion or withdrawal. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (ie, the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the dosage specified in the package insert (including overdosing, underdosing, abuse, and withdrawal) treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the dosing schedule defined in the package insert), 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. Definition of under- and overdosing is done as per the judgement of the treating physician.

Any pregnancy that occurs after administration of medicinal product will be reported on a Pregnancy Form and followed-up at 1 year post-delivery, if feasible.

11.1.2.1 Severity

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

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

11.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the medicinal product/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 medicinal productand the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not associated with the medicinal product (ie, does not follow a reasonable temporal relationship to the administration of product 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 medicinal product
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of medicinal product
  - An alternative etiology is equally or less likely compared to the potential relationship to the medicinal product
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of medicinal product 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 product as evidenced by measurement of the product 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 and occurring within 30 days, the investigator shall provide the alternative etiology.

11.2 Non-Medical Complaints

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

- A failure of a product to exhibit its expected pharmacological activity and/or design function
- Missing components
- Damage to the product or unit carton
- A mislabeled product (potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product that causes 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 MAH within 1 business day. If requested, defective product(s) will be returned to the MAH for inspection and analysis according to procedures.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The investigator will comply with the publication policy as described in the Non-interventional Trial Agreement.

The investigator, or coordinating investigator(s) for multicenter studies, will sign the study report

13. REFERENCES

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14. ANNEXES

14.1 List of Stand-Alone Documents

No.	Date	Title
1	TBD	Study Roster
2	TBD	Clinical Monitoring Plan
3	TBD	Data Management Plan
4	TBD	Stastistical Analysis Plan

14.2 ENCePP Checklist for Study Protocols

Refer to the completed ENCePP Checklist.

14.3 Additional Information

List of Definitions

Important terms	Definitions
Chronic pain:	Continuous and/or intermittent pain, related to the pathophysiology of hemophilia, requiring intervention (pharmacological or non-pharmacological treatment), and in which the cause of pain cannot be readily removed, occurring more than once a week and lasting 3 months or more"
Episodic prophylaxis	Episodic prophylaxis lasting no more than 3 months.
High responding inhibitors:	"inhibitors with peak activity >5 Bethesda Units (BU/mL) associated with anamnesis following replacement of the missing clotting factor." and this level >5 BU/mL "is maintained at any time".
On-demand treatment	Treatment of acute bleeds with any factor concentrates with the goal to resolve bleeds
Prophylaxis	Regular administration of factor concentrates with the goal to prevent bleeds. For analysis purposes, in this prototol, Hemophilia B prophylaxis is defined as follows: at least one administration per week. Long term prophylaxis lasting for one year or more. Short term prophylaxis lasting for more than 3 months.
Target Joint	A target joint is defined as a joint in which at least 3 or more spontaneous bleeds into a single joint within a consecutive 6 month period. Where there have been ≤ 2 bleeds into the joint within a consecutive 12 month period the joint is no longer considered a target joint (Blanchette et al 2014) [19]

APPENDIX 1

Assessment of effectiveness

Total number (%) of treated bleeds and their corresponding hemostatic effectiveness ratings using an "excellent-to-poor" 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 3
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.
Fair	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.
Poor	No improvement of signs or symptoms or conditions worsen.

For prevention of bleeding episodes:

Annualized (ABR) and/or montly bleeding rate (MBR), all bleeds, will be calculated as appropriate, based on the following formula: ABR = (number of bleeds/observational period days)*365.25; MBR = (number of bleeds/observational period – days)*30.44

- ✓ ABR and/or MBR will be calculated as appropriate, in all joint bleeding events
- ✓ Assessment of hemostatic effectiveness
  - The effectiveness will be assessed by a "excellent-to-poor" 4-point Likert scale by the subjects/care-giver (subjects <12 years: care-giver, subjects ≥ 12 years: self assessment) at the end of each prophylaxis period (if possible rated within 24 hours from the end of the prophylactic treatment) or on an annual basis, whichever occurs first.

Table 4 **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-
Fair	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
Poor	Frequent breakthrough bleeding episodes interfering with activity level and quality of life. Not satisfied with the treatment.

APPENDIX 2

The Hemophilia Joint Health Score (HJHS) [17] was developed by the International Prophylaxis Study Group (IPSG) as a new scoring system for musculoskeletal evaluation optimized for use in children with no or minimal joint disease. The HJHS is better suited for children aged 4–18 years and all patients on primary prophylaxis than the Gilbert score, which was found to be too insensitive to identify earliest signs of joint disease. The HJHS includes the following parameters: swelling, duration of swelling, muscle atrophy, joint pain, crepitus on motion, flexion loss, extension loss, strength and global gait. The HJHS measures joint health, in the domain of body structure and function (i.e. impairment), of the joints most commonly affected by bleeding in hemophilia: the knees, ankles, and elbows. It can be used when there is a need for orthopedic intervention, or as an outcome measure of physiotherapy interventions. It is appropriate for monitoring joint change over time or assessing effectiveness of treatment regimens in children receiving both prophylactic and on-demand therapy. The HJHS 2.1 provides a total score (higher score is worse; max=124), joint specific scores, and a global gait score. See Table 5. The HJHS total score, calculated from the Sum of Joint Totals and Global Gait Score will be collected during screening, annual, and termination visits or whenever the treating physician deems it appropriate.

Table 5 **Hemophilia Joint Health Score (HJHS) for assessing Joint Impairment**	
Swelling	0 = no swelling 1 = mild 2 = moderate 3 = severe
Duration (swelling)	0 = no swelling or < 6 months 1 = ≥6 months
Muscle Atrophy	0 = none 1= mild 2 = severe
Joint Pain	0 = no pain through active range of motion 1 = no pain through active range, only pain on gentle overpressure or palpation 2 = pain through active range
Crepitus on Motion	0 = none 1= mild 2 = severe
Flexion Loss	0 = < 5° 1= 5° - 10° 2 = 11° - 20°3 = > 20°
Extension Loss **(from hyperextension)**	0 = < 5° 1= 5° - 10° 2 = 11° - 20° 3 = > 20°
Strength **(using the Daniels &Worthingham'scale)**	Within available ROM 0 = holds test position against gravity with maximum resistance (gr.5) 1 = holds test position against gravity with moderate resistance (but breaks with maximal resistance) (gr.4) 2 = holds test position with minimal resistance (gr.3+), or holds test position against gravity (gr. 3) 3 = able to partially complete ROM against gravity (gr.3-/2+), or through partial ROM gravity eliminated (gr.2-) 4 = Trace (gr.1) or no muscle contraction (gr.0) NE = non-evaluable
Global Gait **(walking, stairs, running, hopping on 1 leg)**	0 = all skills are within normal limits 1 = one skill is not within normal limits 2 = two skills are not within normal limits 3 = three skills are not within normal limits 4 = four skills are not within normal limits NE = non-evaluable

Source: Feldman et al, 2008, HJHS Summary Score Sheet at (last accessed August 2014)
http://www1.wfh.org/docs/en/Publications/Assessment_Tools/HJHS_Summary_Score.pdf

- Radiographs using the Pettersson scale (if available)
- The World Federation of Hemophilia endorsed a radiographic scale, commonly referred to as the Pettersson scale [18] to measure hemophilia joint health status. Eight parameters are weighted and summed to give a score for the joint as shown in Table 6. Pettersson scores of all joints will be collected during screening, intervals, and termination visits or whenever the treating physician deems it appropriate.

Table 6
Pettersson Scale for Radiographic Evaluation of Hemophilic Joints

X-Ray	Osteoporosis: Absent: 0 Present: 1 Enlarged epiphysis: Absent: 0 Present: 1 Irregular subchondral surface: Absent: 0 Surface partially involved: 1 Surface totally involved: 2 Narrowing of joint space: Absent: 0 Present with joint space <1 mm: 1 Present with joint space >1 mm: 2 Subchondral cyst formation: Absent: 0 1 cyst: 1 >1 cyst: 2 Erosion at joint margins: Absent: 0 Present: 1 Gross incongruence of articulating bone ends: Absent: 0 Slight: 1 Pronounced: 2 Joint deformity (angulation and/or displacement between articulating bones): Absent: 0 Slight: 1 Pronounced: 2

Source: Pettersson H et al 1980 [18]

- Magnetic Resonance Imaging scoring system (if available and used at site)
- Several MRI scoring systems have been developed to measure hemophilia joint health status. One of the most commonly used systems was one that was developed in Lund, Sweden [23]. MRI scores of all joints will be collected during screening, intervals, and termination visits or whenever the treating physician deems it appropriate. The scoring system [24;25;26] used shall be determined by the subject's radiologist.

Table 7
Magnetic Resonance Imaging Scoring System Developed in Lund, Sweden

A Component	Subchondral Cyst
	Present in at least 1 bone Present in at least 2 bones >3 cysts in at least 1 bone >3 cysts in at least 2 bones Largest size >4 mm in at least 1 bone Largest size >4 mm in at least 2 bones
	Irregularity/erosion of subchondral cortex
	Present in at least 1 bone Present in at least 2 bones Involve more than half of joint surface in at least 1 bone Involve more than half of joint surface in at least 2 bones
	Chondral destruction
	Present in at least 1 bone Present in at least 2 bones Full thickness defect in at least 1 bone Full thickness defect in at least 2 bones Full thickness defect involve
	s >1/3 of joint surface in at least 1 bone
Effusion/hemarthrosis (e)	Full thickness defect involves >1/3 of joint surface in at least 2 bones
Hypertrophic synovial (s)	0 absent
Hemosiderin (h)	1 equivocal
	2 small
	3 moderate
	4 large

Source: Lundin B et al. 2004 [23]

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PARIXS

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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, Non-interventional 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.

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