Amsterdam, 25 January 2024
EMA/101747/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rixubis

International non-proprietary name: Nonacog gamma

Procedure no.: EMEA/H/C/003771/P46/007

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
☐	Start of procedure	11 Sep 2023	11 Sep 2023	☐
☐	CHMP Rapporteur Assessment Report	16 Oct 2023	16 Oct 2023	☐
☐	CHMP members comments	30 Oct 2023	30 Oct 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	06 Nov 2023	n/a	☐
☐	CHMP adoption of conclusions:	09 Nov 2023	09 Nov 2023	☐
☐				☐
☐	Re-start			☐
☐	CHMP Rapporteur Assessment Report	10 Jan 2024	10 Jan 2024	☐
☐	CHMP members comments	15 Jan 2024	15 Jan 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	18 Jan 2024	n/a	☐
☒	CHMP adoption of conclusions:	25 Jan 2024	25 Jan 2024	☐

Declarations

☒ The assessor confirms that this assessment does **not** include non-public information, including commercially confidential information (e.g. ASMF, information shared by other competent authorities or organisations, reference to on-going assessments or development plans etc), irrespective from which entity was received.

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1. Introduction

On 28 Aug 2023, the MAH submitted a completed paediatric study for Rixubis (nonacog gamma), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A Clinical Addendum Overview (Module 2), a Clinical Study Report with Appendices and an Erratum (all Module 5) are provided for study 251602.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study 251602 (study title: Phase IV Multi-center, Prospective, Interventional, Post-marketing Study in Hemophilia B Patients in India receiving RIXUBIS as On-demand or Prophylaxis Under Standard Clinical Practice) is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

RIXUBIS is a coagulation factor IX (FIX) product. It is a purified protein produced utilizing recombinant deoxyribonucleic acid technology. It has a primary amino acid sequence that is identical to the Ala-148 allelic form of plasma-derived FIX, and its structural and functional characteristics are comparable to endogenous FIX. Factor IX is activated by factor VIIa/tissue factor complex in the extrinsic pathway and by factor XIa in the intrinsic coagulation pathway. Activated FIX, in combination with activated factor VIII, activates factor X. This results ultimately in the conversion of prothrombin to thrombin. Thrombin then converts fibrinogen into fibrin, and a clot can be formed.

RIXUBIS contains the active substance nonacog gamma and is a coagulation FIX product that is produced by recombinant technology, ie, by using modern gene replication technologies. RIXUBIS is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line.

RIXUBIS has been approved for the treatment and prevention of bleeding episodes in patients with hemophilia B (congenital FIX deficiency), routine prophylaxis of bleeding episodes in patients with hemophilia B, and perioperative management of bleeding in patients with hemophilia B in 21 countries/regions (approved via centralized procedure in the European Union [EU]) as of 30 Jun 2022.

The product is available as powder and solvent for solution for injection in the following strengths: 250 international units (IU), 500 IU, 1000 IU, 2000 IU, and 3000 IU. The strengths and indications for use of RIXUBIS may vary in different countries. RIXUBIS is formulated as a sterile, non-pyrogenic, white or off-white, lyophilized powder and solvent for solution for intravenous injection and is stabilized with a mixture of sugars and salts. Dosage and duration of treatment with RIXUBIS depend on the severity of the FIX deficiency, the location and extent of bleeding, the patient's clinical condition and age, and pharmacokinetic (PK) parameters of FIX, such as incremental recovery (IR) and half-life.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for: Study 251602: Phase IV Multi-center, Prospective, Interventional, Post-marketing Study in Hemophilia B Patients in India receiving RIXUBIS as On-demand or Prophylaxis Under Standard Clinical Practice

2.3.2. Clinical study

Study 251602: Phase IV Multi-center, Prospective, Interventional, Post-marketing Study in Hemophilia B Patients in India receiving RIXUBIS as On-demand or Prophylaxis Under Standard Clinical

Study Period:

Study Initiated (first subject enrolled): 07 Dec 2018

Study Completed (last subject completed): 11 Aug 2021

Date of the Report: 27 Jul 2022

Description

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

The purpose of this addendum is to summarize results from completed Study 251602, a Phase 4, multicenter, prospective, interventional, postmarketing study in hemophilia B previously treated patients (PTPs) in India receiving RIXUBIS under standard clinical practice.

The primary objective of the study was to assess the safety of RIXUBIS based on serious adverse events (SAEs) (including FIX inhibitors). Secondary safety objectives included the occurrence of adverse events (AEs), changes in laboratory parameters, and immunogenicity (excluding FIX inhibitors). Secondary efficacy objectives included the assessment of the efficacy of prophylactic treatment with RIXUBIS and efficacy of RIXUBIS in the control of bleeding episodes.

The safety and efficacy of RIXUBIS under standard clinical practice were evaluated in a total of 25 evaluable hemophilia B subjects. All study subjects were included in the assessments of safety (safety analysis set [SAS]) and hemostatic effectiveness (effectiveness full analysis set [EFAS]). Out of the 25 subjects, 23 (92%) subjects received at least 3 months of prophylactic treatment in the study and were included in the efficacy analysis. No on-demand subjects were enrolled.

Overall, RIXUBIS was found to be safe and effective in hemophilia B PTPs who received RIXUBIS treatment under standard clinical practice in India. Although there was a high percentage of protocol deviations reported during the study, these deviations did not compromise subjects' safety or efficacy, nor were there any concerns pertaining to study validity. Results from this study are consistent with previous real-world evidence and clinical trial data.

The total of 23/25 prophylaxis subjects in India who completed the study provide sufficient evidence for safety and efficacy of RIXUBIS in hemophilia B PTPs treated under standard clinical practice in India. The results of Study 261502 did not change the positive benefit-risk profile of RIXUBIS.

Methods

Study participants

Inclusion Criteria

Each subject had to meet all the following criteria to be eligible for the study:

1. Subject or legally authorized representative (LAR) (in case of study participants <18 years of age) gave written informed consent to participate in the study.

2. Subject had hemophilia B.

3. Subject was defined as PTP:

- Subject aged ≥6 years that had been previously treated with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 150 exposure day (EDs).
- Subject aged <6 years that had been previously treated with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 50 EDs.

4. Subject had no evidence of a history of FIX inhibitors.

5. Subject was human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥200 cells/mm3, as confirmed by central laboratory at screening.

6. Subject was hepatitis C virus negative (HCV-) by antibody or polymerase chain reaction (PCR) testing (if positive, antibody titer confirmed by PCR), as confirmed by central laboratory at screening; or HCV+ with chronic stable hepatitis.

7. Subject was willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

1. Subject had known hypersensitivity or presence of any contraindication to RIXUBIS or its excipients including hamster protein.

2. Subject had evidence of an ongoing or recent thrombotic disease, fibrinolysis or disseminated intravascular coagulation (DIC).

3. Subject had a history of FIX inhibitors with a titer ≥0.6 Bethesda unit (BU) (as determined by the Nijmegen modification of the Bethesda assay or the assay, employed in the respective local laboratory) at any time prior to screening.

4. Subject had a detectable FIX inhibitor at screening, with a titer ≥0.6 BU as determined by the Nijmegen modification of the Bethesda assay in the central laboratory.

5. Subject had severe chronic liver disease as evidenced by, but not limited to, any of the following: International Normalized Ratio (INR) >1.4, hypoalbuminemia, portal vein hypertension including presence of otherwise unexplained splenomegaly and history of esophageal varices.

6. Subject had severe chronic hepatic dysfunction [eg, ≥5 times upper limit of normal alanine aminotransferase (ALT), as confirmed by central laboratory at screening, or a documented INR >1.5].

7. Subject had severe renal impairment (serum creatinine >2.0 mg/dL), as confirmed by central laboratory at screening.

8. Subject had been diagnosed with an inherited or acquired hemostatic defect other than hemophilia B.

9. Subject's platelet count was <100,000/mL.

10. Subject had a clinically significant medical, psychiatric, or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject's safety or compliance.

11. Subject was receiving or scheduled to receive during the course of the study, an immunomodulating drug (eg, corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day, or α-interferon) other than antiretroviral chemotherapy.

12. Subject participated in another clinical study involving an investigational product (IP) or investigational device within 30 days prior to enrollment or was scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.

13. Subject was a family member or employee of the investigator.

Treatments

All subjects received exclusively RIXUBIS. The physician was expected to follow standard clinical practice. The treatment with RIXUBIS was administered at the discretion of the investigator and consisted of either prophylaxis or on-demand. As discussed in the RIXUBIS Product Label for India, incremental recovery (IR) is used for the dosing calculation for the on-demand treatment of bleeding episodes. In this study no on-demand subject was enrolled, therefore IR was not calculated.

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

RIXUBIS is formulated as a sterile, nonpyrogenic, lyophilized powder of concentrated rFIX for intravenous injection and is provided in a single-dose vial labeled with the rFIX activity expressed in international unit (IU). Subjects used the commercial material for this study. RIXUBIS was infused intravenously after reconstitution with Sterile Water for Injection (SWFI). The infusions were administered by intravenous infusion at a maximum infusion rate of 10 mL/minute. It was recommended to infuse the first dose of RIXUBIS in the clinic. All subjects enrolled in the study were treated as per standard clinical practice. In all cases, the treatment with RIXUBIS was at the discretion of the investigator and consisted of either a prophylactic or on-demand treatment as per the RIXUBIS Product Label for India.

The RIXUBIS batch numbers used in this study are provided below:

- RIXUBIS Coagulation Factor IX (Recombinant) 250 IU/vial (Kit): TNA17007AL-0248, TNA17011AG-05, TNA16013AK-01

- RIXUBIS Coagulation Factor IX (Recombinant) 500 IU/vial (Kit): TNA17004AL-0249, TNA18005AH-06, TNA16007AP-02, TNA16007AP-02, TNA18013AQ-0826, TNA18009AE-0666, TNA18013AC-0665, TNA17017AI-0440, TNA17017AI-0537, TNA17019AC-0441
- RIXUBIS Coagulation Factor IX (Recombinant) 2000 IU/vial (Kit): TNA18021AC-0250, TNA18014AB-07, TNA17002AG-03, TNA17002AG-04

Duration of Treatment:

The overall duration of the study was 36 months from study initiation (ie, first subject enrolled) to study completion (ie, last subject last visit).

The follow-up period for each enrolled subject was up to 6 months from baseline while on treatment. The following visits were performed: Baseline, 1 month, 3 months, and 6 months. Subjects were discontinued from the study after they had been in the study for 6 months, irrespective of the RIXUBIS EDs they had received during that 6-month treatment period.

Objective(s)

Primary Objective

The primary objective of the study was to assess the safety of RIXUBIS based on serious adverse events (SAEs) (including FIX inhibitors).

Secondary Objectives

Safety:

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

Efficacy

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

Outcomes/endpoints

Primary Outcome Measure

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

Secondary Outcome Measures

Safety:

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

summarized.

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

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

Efficacy:

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

Sample size

Based on data from the WFH from 1998-2006, the mean prevalence of hemophilia B in India was 0.19 per 100,000 male. In the WFH Report on the Annual Global Survey 2014, there were a total of 14,450 cases of hemophilia and 2,281 confirmed cases of hemophilia B in India in 2014. Due to the low prevalence of hemophilia B and difficulty in switching patient from current therapy, an estimated study size of 25 subjects will be recruited.

Randomisation and blinding (masking)

Not applicable as study 251602 was an open-label single arm study.

Statistical Methods

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

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

<u>Analysis Sets</u>

Effectiveness Full Analysis Set (EFAS):

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

Safety Analysis Set (SAS):

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

<u>Handling of Missing, Unused, and Spurious Data</u>

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

Methods of Analysis

Primary Outcome Measure:

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

Secondary Outcome Measures:

Safety

- The number of possibly or probably related adverse events as well as the number of subjects with possibly or probably related adverse events that occurred during or after first RIXUBIS infusion will be summarized.
- Shift tables will be presented for the results of clinical laboratory data.
- Subjects developing binding IgG or IgM antibodies to FIX or antibodies to CHO proteins or rFurin will be summarized.

Efficacy

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

Planned Interim Analysis of the Study

No interim analyses are planned for this study.

Changes in the Conduct of the Study

The study protocol was amended twice: Amendment 1 dated 15 Sept 2016 and Amendment 2 dated 27 Sep 2017.

Summary of Changes from Amendment 1 to Amendment 2 is provided below:

Description of Change: The earlier version (Protocol Amendment 1, dated 15 Sep 2016) used the Post-Marketing Surveillance (PMS) study protocol template. An Interventional study protocol template was used for this amendment. These 2 protocol templates (PMS study protocol template and Interventional study protocol template) are very different and almost all sections were changed as a result.

Purpose for Change: Since we were providing IP free of cost and since we were doing a mandatory inhibitor testing as per the recommendation from the Indian Health Authority, this study was considered an Interventional study.

Changes in the Planned Analyses

The original SAP dated 22 Nov 2019 was amended once on 29 Sep 2021. All the changes were made to align with the dry run analysis.

The details of changes in planned analysis are presented below:

- Visit windows were not derived. Assessments were assigned to visits based on the information reported in the completed eCRF page at each planned visit.
- Analysis of ABR with prophylactic use of RIXUBIS were clarified: Zero was considered as a possible number of unique bleeds. All subjects on prophylaxis treatment for at least 3 months were included in the summary of ABR.
- For analysis of FIX Nijmegen, negative result was defined as any value <0.6 BU.
- COVID-19 related protocol deviations were summarized.

Results

Participant flow/Recruitment

Among the 31 subjects who were screened, 25 subjects met all eligibility criteria (included in EFAS) and received RIXUBIS treatment (included in SAS). Of all the included subjects, 23 (92.0%) subjects completed the study. Of those subjects who discontinued from the study (n=2, 8.0%); 1 (4.0%) subject discontinued due to physician decision and 1 (4.0%) subject discontinued for 'other' reason.

Table 1: Subjects Disposition (All Screened Subjects)

	Total n (%)
Screened Set	31
Effectiveness Full Analysis Set (EFAS)[a]	25 (100)
Safety Analysis Set (SAS)[b]	25 (100)
Subject Completed the Study	23 (92.0)
Subject Discontinued from the Study	2 (8.0)
Primary Reason for Discontinuation of Study	
Subject Had Adverse Event(s)	0
Physician Decision	1 (4.0)
Withdrawal by Subject/Legally authorized representative	0
Study Terminated by Sponsor	0
Other	1 (4.0)

EFAS=effectiveness full analysis set; n=Number of subjects with available data; SAS=Safety Analysis Set
% = Percentage of subjects (n) based on the Effectiveness Full Analysis Set.
Other: Subject discontinuation due to non-compliance of Investigational Product.
[a] All enrolled subjects who met all eligibility criteria.
[b] All enrolled subjects who received RIXUBIS at any time during the study.

Protocol Violations/Deviations

Among all included subjects, there were 21 (84.0%) subjects with a total of 124 deviations reported. There were 4 (16.0%) subjects with any critical deviations (m=6; m stands for number of protocol deviation), 19 (76.0%) subjects with any major deviations (m=96), and 14 (56.0%) subjects with any minor deviations (m=22). There were 3 (12.0%) subjects who had any deviations (m=5) related to COVID-19, of which 2 (8.0%) subjects had any major deviations (m=4), and 1 subject (4.0%) had any minor deviation (m=1).

The most common critical deviation was related to IP compliance (n=4, 16.0%; m=5). Most of the major protocol deviations were also related to IP compliance (n=15, 60.0%; m=83), followed by visit schedule criteria (n=6, 24.0%; m=9), laboratory assessment criteria (n=3, 12.0%; m=3), and randomization / enrollment criteria (n=1, 4.0%; m=1). Most of the minor protocol deviations were related to visit schedule criteria (n=10, 40.0%; m=12) followed by laboratory assessment criteria (n=5, 20.0%; m=6), eligibility and entry criteria (n=2, 8.0%; m=2), and IP compliance (n=2, 8.0%; m=2). All COVID-19 related protocol deviations were related to visit schedule criteria (n=3, 12%; m=5).

Baseline data

Demographics

All subjects were included in both EFAS and SAS. The mean (SD) age at enrolment was 24.6 (8.29) years and mean (SD) BMI was 20.6 (3.81) kg/m2. Most subjects were of age group ≥18 years (n=20, 80.0%). All included subjects were male. All subjects were not-Hispanic or Latino and most subjects were of Indian origin (n=24, 96.0%).

Table 2: Demographic and Baseline Characteristics (EFAS and SAS)

Characteristic	EFAS (N=25)	SAS (N=25)
Demographic		
Age (years)[a]		
n	25	25
Mean (SD)	24.6 (8.29)	24.6 (8.29)
Median	22.0	22.0
Q1, Q3	20.0, 28.0	20.0, 28.0
Min, Max	12.0, 48.0	12.0, 48.0
Age Category 1 (years) [n (%)]		
<12	0	0
≥12	25 (100)	25 (100)
Age Category 2 (years) [n (%)]		
<6	0	0
≥6 to <12	0	0
≥12 to <18	5 (20.0)	5 (20.0)
≥18	20 (80.0)	20 (80.0)
Gender [n (%)]		
Male	25 (100)	25 (100)
Female	0	0
Child-bearing Potential [n (%)][b]		
Yes	0	0

No	0	0
Ethnicity [n (%)]		
Hispanic or Latino	0	0
Not Hispanic or Latino	25 (100)	25 (100)
Not Reported	0	0
Race [n (%)]		
American Indian or Alaska Native	0	0
Asian	24 (96.0)	24 (96.0)
Indian	24 (96.0)	24 (96.0)
Non-Indian	0	0
Black or African American	0	0
Native Hawaiian or Other Pacific Islander	0	0
White	0	0
Multiple	1 (4.0)	1 (4.0)
Baseline[c]		
Height (cm)		
n	25	25
Mean (SD)	164.6 (5.74)	164.6 (5.74)
Median	163.0	163.0
Q1, Q3	161.0, 168.0	161.0, 168.0
Min, Max	155.0, 178.0	155.0, 178.0
Weight (kg)		
n	25	25
Mean (SD)	56.0 (12.04)	56.0 (12.04)
Median	53.6	53.6
Q1, Q3	47.6, 62.0	47.6, 62.0
Min, Max	40.0, 88.1	40.0, 88.1
BMI (kg/m^2)		
n	25	25
Mean (SD)	20.6 (3.81)	20.6 (3.81)
Median	19.8	19.8
Q1, Q3	18.1, 22.2	18.1, 22.2
Min, Max	14.9, 30.1	14.9, 30.1

BMI=Body Mass Index; EFAS=Effectiveness Full Analysis Set; eCRF=electronic case report form; Max=Maximum; Min=Minimum; Q1: First Quartile; Q3=Third quartile; SAS=Safety Analysis Set; SD=Standard deviation
n=Number of subjects with available data; N=Total number of subjects in the EFAS or SAS; as appropriate.
% = Percentage of subjects (n) based on subjects with available (non-missing) data within the EFAS or SAS, as appropriate.
BMI is calculated as BMI (kg/m^2) = weight (kg) / (height $(m)^2$).
[a] Age as calculated on the eCRF based on the date of birth.
[b] Percentage of female subjects.
[c] The baseline value for a characteristic is the value from the baseline visit as specified in the SAP.

Medical History

Overall, 8 (32.0%) subjects had any medical history or condition. Four of these subjects had a history of musculoskeletal disease and 2 subjects each had a history of gastrointestinal and neurological diseases. Most of the medical history reported was mild or moderate; 1 subject had severe musculoskeletal disorder (bilateral knee replacement). None of subjects reported history of any surgery.

Table 3: Medical History by Body System (EFAS)

Body System[a] Severity[b]	Total (N=25) n (%)
Any Medical History or Condition	8 (32.0)
Gastrointestinal	2 (25.0)
Mild	1 (50.0)
Moderate	1 (50.0)
Severe	0
Musculoskeletal	4 (50.0)
Mild	2 (50.0)
Moderate	2 (50.0)
Severe	1 (25.0)
Neurological	2 (25.0)
Mild	0
Moderate	2 (100)
Severe	0
Any Surgery	0

EFAS=effectiveness full analysis set; n=Number of subjects with available data; N=Total number of subjects in the EFAS
Subjects were counted once per system organ class at the maximum severity.

[a] Percentages are based on number of subjects who reported any Medical History or Condition.

[b] Percentages for the severity are based on the observed number of subjects in a specific body system within Effectiveness Analysis Set.

Hemophilia B History

The mean (SD) age of hemophilia B diagnosis was 5.9 (6.96) years. The mean (SD) time since diagnosis of hemophilia B was 19.2 (8.22) years. No subject reported a history of thromboembolism, allergic reaction, or inhibitors of FIX. A total of 2 (8.0%) subjects reported a family history of inhibitors of FIX.

Table 4: Hemophilia B History (EFAS)

	Total (N=25)
Age at Diagnosis of Hemophilia B (years)[a]	
n	25
Mean (SD)	5.9 (6.96)
Median	2.50
Q1, Q3	0.7, 9.2
Min, Max	0.1, 23.2
Time since Diagnosis of Hemophilia B (years)[b]	
n	25
Mean (SD)	19.2 (8.22)
Median	19.70
Q1, Q3	14.6, 25.4
Min, Max	5.9, 36.7
History of Thromboembolism [n (%)]	
Yes	0
No	23 (92.0)
Unknown	2 (8.0)
History of Allergic Reactions [n (%)]	
Yes	0
No	24 (96.0)
Unknown	1 (4.0)
History of Inhibitors of Factor IX [n (%)]	
Yes	0
No	24 (96.0)
Unknown	1 (4.0)
Family History of Inhibitors of Factor IX [n (%)]	
Yes	2 (8.0)
No	22 (88.0)
Unknown	1 (4.0)

EFAS=effectiveness full analysis set; eCRF=electronic Case Report Form; Max=Maximum; Min=Minimum; Q1=First Quartile; Q3=Third quartile; SD=Standard deviation
"Unknown" category is when there is no entry in the medical record relating to item (category in the eCRF).
n = Number of subjects with available data.
N = Total number of subjects in the EFAS
% = Percentage of subjects (n) based on subjects with available (non-missing) data within the EFAS.
[a] Age at Diagnosis of Hemophilia B (years) = (Date of Hemophilia B Diagnosis - Date of Birth + 1) / 365.25
[b] Time since diagnosis of Hemophilia B (years) = (Inform Consent date – Date of Hemophilia B Diagnosis + 1) / 365.25

Hemophilia B Treatment History

The mean (SD) average ABR based on previous 3 to 6 months was 19.2 (28.88) bleeds per year. A total of 3 (12.0%) subjects had received on-demand FIX replacement therapies within the 6 months prior to enrolling in the study (2 subjects received Immunine/Baxalta and 1 subject received Leflunomide/Baxalta). Each bleeding episode required 1 treatment. The mean (min, max) average dose required to treat bleeding episodes was 410.0 (329.09) IU/kg. All subjects had "Good" to "Moderate" response to treatment. The mean (SD) duration of on-demand treatment was 217.7 (39.19) months.

Table 5: Hemophilia B Treatment History (EFAS)

	Total (N=25)
Average ABR Based on Previous 3-6 Months (Bleeds per Year)	
n	25
Mean (SD)	19.2 (28.88)
Median	10.0
Q1, Q3	8.0, 20.0
Min, Max	3, 150
Missing	0
Any FIX Replacement Therapies Used Within the Last 6 Months [n (%)]	
Yes	3 (12.0)
No	22 (88.0)
Missing	0
If Yes:	
FIX Product status [n (%)]	
Commercial Product	3 (100)
Investigational Product	0
Missing	0
FIX Product/ manufacturer [n (%)]	
Immunine/Baxalta	2 (66.7)
Leflunomide/Baxalta	1 (33.3)
Missing	0
FIX Treatment Type [n (%)]	
Prophylaxis	0
On-demand	3 (100)
Missing	0
If Prophylaxis:	
Dose per infusion (IU/kg)	
n	0
Mean (SD)	0
Median	0
Q1, Q3	0
Min, Max	0
Missing	0
Frequency (times per week)	
n	0
Mean (SD)	0
Median	0
Q1, Q3	0
Min, Max	0
Missing	0
Duration of Prophylaxis Treatment (months)[a]	
Mean (SD)	0

Median	0
Q1, Q3	0
Min, Max	0
If On-demand treatment:	
Average Dose Required to Treat Bleed (IU/kg)	
n	3
Mean (SD)	410.0 (329.09)
Median	600.0
Q1, Q3	30.0, 600.0
Min, Max	30, 600
Missing	0
Estimated Average Number of Infusions for Each Bleeding Episode	
n	3
Mean (SD)	1.0 (0.00)
Median	1.0
Q1, Q3	1.0, 1.0
Min, Max	1, 1
Missing	0
Usual Response to Treatment [n (%)]	
Excellent	0
Good	2 (66.7)
Moderate	1 (33.3)
None	0
Unknown	0
Missing	0
Duration of On-demand Treatment (months)[b]	
n	3
Mean (SD)	217.7 (39.19)
Median	228.6
Q1, Q3	174.3, 250.3
Min, Max	174, 250
Missing	0

ABR=Annualized bleeding rate; EFAS=effectiveness full analysis set; eCRF=electronic Case Report Form; FIX=recombinant factor IX; IU=international unit; max=Maximum; Min: Minimum; Q1=First Quartile; Q3=Third quartile; SD=Standard deviation
"Unknown" category is when there is no entry in the medical record relating to item (category in the eCRF) and the "Missing" category is when there is no data available.
n = Number of subjects with available data. N = Total number of subjects in the EFAS.
% = Percentage of subjects (n) based on subjects with available (non-missing) data within the EFAS.
Data entered as "Immunine/Baxalta" or "Immunine/Baxter" were combined into 1 row, as they are the same treatment.
[a] Duration of prophylaxis treatment (months) = (Prophylaxis End Date – Prophylaxis Start Date + 1) / 30.4375.
[b] Duration of on-demand treatment (months) = (On-demand End Date – On-demand Start Date + 1) / 30.4375.

Prior and Concomitant Medications

Prior Medications

There was only 1 subject who received any prior medication (ie, blood coagulation factor [eftrenonacog alfa]). Similarly, only 1 subject received prior non-drug therapies for FIX deficiency.

Concomitant Medications

Overall, 4 subjects (16.0%) received concomitant medications. The most common concomitant medications were tranexamic acid (n=2, 8.0%) and combination of paracetamol and tramadol hydrochloride (n=2, 8.0%) followed by antivirals for treatment of HCV infections (daclatasvir and sofosbuvir, n=1, 4.0% each), rabeprazole sodium (n=1, 4.0%), and herbal anti-inflammatory and antirheumatic remedies (n=1, 4.0%).

No subject received any concomitant non-drug therapies or concomitant procedures.

Table 6: Concomitant Medication (EFAS)

Therapeutic Class Preferred Term	Total (N=25) n (%) m
Any Concomitant Medications	4 (16.0) 8
Amino Acids	2 (8.0) 2
Tranexamic Acid	2 (8.0) 2
Antivirals For Treatment Of HCV Infections	1 (4.0) 2
Daclatasvir	1 (4.0) 1
Sofosbuvir	1 (4.0) 1
Herbal Anti-inflammatory And Antirheumatic Remedies	1 (4.0) 1
Boswellia Serrata; harpagophytum Procumbens;rosa Canina	1 (4.0) 1
Opioids In Combination With Non-Opioid Analgesics	2 (8.0) 2
Paracetamol; tramadol Hydrochloride	2 (8.0) 2
Proton Pump Inhibitors	1 (4.0) 1
Rabeprazole Sodium	1 (4.0) 1

EFAS=effectiveness full analysis set; HCV=hepatitis C virus; n=Number of subjects with available data; m=Number of concomitant medication administrations; N=Total number of subjects in the EFAS
Subjects were counted once per category.
Concomitant medications are defined as any medication with a start date prior to the date of the first dose of RIXUBIS and continuing after the first dose of RIXUBIS, or, with a start date between the dates of the first and last doses of RIXUBIS, inclusive.

Number analysed

A total of 25 hemophilia B subjects were planned and enrolled in this study, of which:

- 25 subjects were included in the Effectiveness Full Analysis Set (EFAS) which comprised of all subjects for whom all inclusion and none of the exclusion criteria were met. This dataset was used for the efficacy analyses.
- 25 subjects were included in the Safety Analysis Set (SAS) which consisted of all subjects having received RIXUBIS at any time during the study.

Efficacy results

Bleeding Episodes

A total of 8 (32.0%) subjects experienced any bleeding episodes during the study. The mean (SD) number of unique bleeding episodes per subject (who experienced any bleeding episodes during the study) was 1.6 (0.74). The total number of unique bleeding episodes was 13 (3 of these unique bleeding episodes occurred prior to starting prophylactic RIXUBIS treatment). Out of 13 unique bleeding episodes, 6 (42.6%) unique bleeding episodes were treated with additional RIXUBIS (1 of the 6 unique bleeding episodes occurred prior to starting prophylactic RIXUBIS treatment). Two (15.4%) subjects received a hemostatic product other than RIXUBIS to treat a bleeding episode and 1 (7.7%) subject received analgesics to treat a bleeding episode.

Table 7: Bleeding Episodes

	Total (N=25)
Did the Subject Experience any Bleeding Episodes During the Study? [n (%)]	
Yes	8 (32.0)
No	17 (68.0)
If Yes:	
Number of Unique Bleeding Episodes Per Subject	
n	8
Mean (SD)	1.6 (0.74)
Median	1.5
Q1, Q3	1.0, 2.0

(EFAS)

Number of Unique Bleeding Episodes Per Subject (category) [n (%)]	
1	4 (50.0)
2	3 (37.5)
3	1 (12.5)
Total Number of Unique Bleeding Episodes	13
Site of Bleeding [n (%)][ab]	
Skin	0
Venipuncture site	0
Muscle	0
Soft Tissue	0
Mucosal	1 (7.7)
Mouth	0
Gum	1 (7.7)
Nose	0
Joint	12 (92.3)
Left Wrist	1 (7.7)
Right Wrist	0
Left Elbow	2 (15.4)
Right Elbow	2 (15.4)
Left Shoulder	1 (7.7)
Right Shoulder	1 (7.7)
Left Hip	0
Right Hip	0
Left Knee	5 (38.5)
Right Knee	2 (15.4)
Left Ankle	0
Right Ankle	2 (15.4)
Body Cavity	0
Hematuria	0
Genitourinary	0
Gastrointestinal	0
Intracranial	0
Other	1 (7.7)
Left Toe	1 (7.7)
Cause of Bleeding [n (%)][a]	
Spontaneous	11 (84.6)
Injury	0
Unknown	2 (15.4)
Missing	0
Severity of Bleeding [n (%)][a]	
Minor	8 (61.5)
Moderate	5 (38.5)
Major	0
Life/Limb threatening	0
Missing	0
Was Treatment with RIXUBIS Required? [n (%)][c]	

Yes	6 (46.2)
No	7 (53.8)
Missing	0
If Yes:	
subject/care-givers Efficacy Rating [n (%)][d]	
Excellent	3 (50.0)
Good	3 (50.0)
Moderate	0
None	0
Missing	0
Did the Investigator agree with the efficacy rating provided by the subject/care-giver?	
Yes	6 (100)
No	0
Missing	0
If No:	
Investigator's Efficacy Rating [n (%)][e]	
Excellent	0
Good	0
Moderate	0
None	0
Missing	0
Did the Subject Receive any Hemostatic Product other than RIXUBIS to Treat this Bleeding Episode? [n (%)][c]	
Yes	2 (15.4)
No	11 (84.6)
Missing	0
Did the Subject Receive any Analgesics to Treat this Bleeding Episode? [n (%)][c]	
Yes	1 (7.7)
No	12 (92.3)
Missing	0

EFAS=Effectiveness Full Analysis Set; eCRF=electronic Case Report Form; Max=Maximum; Min=Minimum; Q1=First Quartile; Q3=Third quartile; SD=Standard deviation
"Unknown" category is when there is no entry in the medical record relating to item (category in the eCRF) and the "Missing" category is when there is no data available.
n = Number of subjects with available data. N = Total number of subjects in the EFAS.
% = Percentage of subjects (n) based on subjects with available (non-missing) data within the EFAS
[a] n = number of unique bleedings within each anatomical site/ cause/ severity of bleeding. Percentage calculated based on the total number of unique bleeding episodes.
[b] The same unique bleeding episode can have more than 1 anatomical site.
[c] n = number of unique bleeding. Percentage calculated based on the total number of unique bleeding episodes.
[d] Percentage calculated based on the total number of unique bleeding episodes that required treatment with RIXUBIS.
[e] Percentage calculated based on the total number of unique bleeding episodes that required treatment with RIXUBIS and investigator did not agree with subject/care-giver Efficacy Rating.

Success rate by Treatment Regimen

All included subjects (n=25) received prophylactic RIXUBIS treatment, and no subjects received on-demand RIXUBIS treatment. Out of the 25 subjects receiving prophylactic RIXUBIS treatment, 8 subjects experienced 13 unique bleeding episodes during the study. Six out of the 13 unique bleeding episodes required additional RIXUBIS treatment and were rated for hemostatic effectiveness. The response to RIXUBIS treatment was rated as "Excellent" for 3 (50.0%) bleeding episodes, and "Good" for 3 (50.0%) bleeding episodes. The rate of success (95% CI) of RIXUBIS treatment was 100% (95% CI: 54.1, 100.0).

Table 8: Success Rate of RIXUBIS for Treatment of Bleeding Episodes by RIXUBIS Treatment Regimen (EFAS)

	On-Demand (N=0)	Prophylaxis (N=25)	Total (N=25)
Number of Subjects with Bleeds During the Study [n*(%)]	0	8 (32.0)	8 (32.0)
Number of Unique Bleeding Episodes During the Study	0	13	13
Number of Unique Bleeding Episodes that required treatment with RIXUBIS	0	6	6
Hemostatic Effectiveness Rating [n (%)][a]			
n	0	6	6
Excellent	0	3 (50.0)	3 (50.0)
Good	0	3 (50.0)	3 (50.0)
Moderate	0	0	0
None	0	0	0
Success [n (%)][b]			
n	0	6	6
Rate of Success[c]	0	6 (100)	6 (100)
95% CI	-, -	54.1,100.0	54.1,100.0

CI=Confidence Interval; EFAS=Effectiveness Full Analysis Set; n=number of unique bleeds; n*=Number of subjects with 1 or more bleeds; N=Total number of subjects in the EFAS

% = Percentage of bleeds (n) based on bleeds within the EFAS.

[a] Hemostatic Effectiveness Rating assessed by subjects, if there is any discrepancy between assessments made by subjects (or the subject's legal representative) and the investigator, assessment made by the investigator shall supersede and be considered the final assessment.

[b] The success of RIXUBIS for treatment of bleeding episodes is defined by grouping the categories of "Excellent"/"Good" of the corresponding hemostatic effectiveness ratings of a 4-point Likert scale ("Excellent", "Good", "Moderate" and "None") by the subjects/care-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.

[c] Percentage based on number of Unique Bleeding Episodes that required treatment with RIXUBIS and were rated.

Success Rate by Bleeding Site

Out of the 25 subjects receiving prophylactic RIXUBIS treatment, 8 (32%) subjects experienced 12 unique bleeding episodes in joints during the study. Six out of the 12 unique bleeding episodes in joints required additional RIXUBIS treatment and were rated for hemostatic effectiveness. The response to RIXUBIS treatment was rated as "Excellent" for 3 (50.0%) bleeding episodes and "Good" for 3 (50.0%) bleeding episodes. The rate of success (95% CI) of RIXUBIS treatment was 100% (95% CI: 54.1, 100.0). Also, there was 1 (4.0%) subject who experienced 1 unique bleeding episode in mucosa, which required additional RIXUBIS treatment, was rated for hemostatic effectiveness. The response to RIXUBIS treatment was rated as "Excellent" and rate of success was 100% (95% CI: 2.5, 100.0). Moreover, there was 1 (4.0%) subject who experienced 1 unique bleeding episode in other site (left toe), which did not require additional RIXUBIS treatment and was not rated for hemostatic effectiveness.

Success Rate by Bleeding Cause

Out of the 25 subjects receiving prophylactic RIXUBIS treatment, 6 (24%) subjects experienced 11 unique bleeding episodes, for spontaneous cause, during the study. Five out of the 11 unique bleeding episodes required additional RIXUBIS treatment and were rated for hemostatic effectiveness. The response to RIXUBIS treatment was rated as "Excellent" for 2 (40.0%) bleeding episodes and "Good" for 3 (60.0%) bleeding episodes. The rate of success (95% CI) of RIXUBIS treatment was 100% (95% CI: 47.8, 100.0).

Two (8.0%) subjects experienced 2 unique bleeding episodes with unknown cause during the study. One out of the 2 unique bleeding episodes required additional RIXUBIS treatment and was rated for hemostatic effectiveness. The response to RIXUBIS treatment was rated as "Excellent" for that bleeding episode. The rate of success (95% CI) of RIXUBIS treatment was 100% (95% CI: 2.5, 100.0).

Success Rate by Bleeding Severity

Out of 25 subjects receiving prophylactic RIXUBIS treatment, 6 (24%) subjects experienced 8 unique bleeding episodes of minor severity during the study. There were no subjects with bleeding episodes of major severity or bleeding episodes with life/limb threatening severity. Three out of 8 unique bleeding episodes required additional RIXUBIS treatment and were rated for hemostatic effectiveness. The response to RIXUBIS treatment was rated as "Excellent" for 2 (66.7%) bleeding episodes and "Good" for 1 (33.3%) bleeding episode. The rate of success (95% CI) of RIXUBIS treatment was 100% (95% CI: 29.2, 100.0).

Also, 3 (12%) subjects experienced 5 unique bleeding episodes of moderate severity during the study. Three out of the 5 unique bleeding episodes required additional RIXUBIS treatment and were rated for hemostatic effectiveness. The response to treatment was rated as "Excellent" for 1 (33.3%) bleeding episode and "Good" for 2 (66.7%) bleeding episodes. The rate of success (95% CI) of RIXUBIS treatment was 100% (95% CI: 29.2, 100.0).

Prophylaxis Efficacy Rating

At an unscheduled visit between the screening visit and Visit 1, only 1 subject received prophylaxis treatment with RIXUBIS and the efficacy rating performed by the investigator was "Excellent".

At Visit 1, all 25 subjects received prophylaxis treatment with RIXUBIS and efficacy ratings were performed in 19 (76.0%) subjects. Most subjects had a "Good" efficacy rating (n=12 [of 19], 63.2%) followed by "Excellent" (n=6 [of 19], 31.6%) and "Moderate" (n=1 [of 19], 5.3%). At an unscheduled visit, between Visit 1 and Visit 2, 1 subject received prophylaxis treatment for which an efficacy rating was not performed.

At Visit 2, 23 (92.0%) subjects received prophylaxis treatment with RIXUBIS and efficacy ratings were performed in 21 (91.3%) subjects. Most subjects had an "Excellent" efficacy rating (n=12 [of 21], 57.1%) followed by "Good" (n=8 [of 21], 38.1%) and "Moderate" (n=1 [of 21], 4.8%).

At the EOT visit, 23 (92.0%) subjects received prophylaxis treatment with RIXUBIS and efficacy ratings were performed in 22 (95.7%) subjects. Most subjects had an "Excellent" efficacy rating (n=14 [of 22], 63.6%) followed by "Good" (n=7 [of 22], 31.8%) and "Moderate" (n=1 [of 22], 4.5%).

No subjects reported a change in prophylaxis treatment or a modification in prophylaxis treatment regimen during the study.

Annualized Bleeding Rate

A total of 10 unique bleeding episodes were reported during prophylaxis (few bleeding episodes occurred prior to prophylaxis treatment). The mean (SD) number of unique bleeds per subject (with a minimum of 3 months prophylactic exposure) was 0.4 (0.79) with a mean treatment duration for prophylactic RIXUBIS treatment of 179.5 (9.08) days. Overall, the mean (SD) ABR in subjects with 3 months prophylaxis RIXUBIS treatment was 0.914 (1.6896).

Table 9: Annualized Bleeding Rate With Prophylactic Use of RIXUBIS (EFAS)

	Total (N=25)
Number of Subjects with Bleeds during prophylaxis [n*(%)]	7 (28.0)
Number of Unique Bleeding Episodes during prophylaxis	10
Unique Bleeds per subject	
n	23
Mean (SD)	0.4 (0.79)
Median	0.0
Q1, Q3	0.0, 1.0
Min, Max	0, 3
Missing	2
RIXUBIS Treatment Duration for Prophylaxis (days)[a]	
n	23
Mean (SD)	179.5 (9.08)
Median	179.0
Q1, Q3	175.0, 183.0
Min, Max	166, 204
Missing	2
Annualized Bleeding Rate (ABR)	
n	23
Mean (SD)	0.914 (1.6896)
Median	0.000
Q1, Q3	0.000, 2.029
Min, Max	0.00, 6.60
Missing	2

ABR=annualized bleeding rate; CSR=clinical study report; EFAS=effectiveness full analysis set; Max=maximum; Min=minimum; Q1=first quartile; Q3=third quartile; SD=standard deviation

n=number of subjects with at least 3-month observation period under prophylaxis treatment regimen; n*=number of subjects with 1 or more bleeds; N=total number of subjects in the EFAS.

%=percentage of subjects (n) based on the EFAS.

Number of unique bleeding episodes=the total number of unique bleeding episodes by subject reported during RIXUBIS treatment for prophylaxis.

Zero is counted as possible number of unique bleeds.

[a] RIXUBIS treatment duration for prophylaxis (days)=SUM (end date of RIXUBIS prophylaxis regimen on the i^{th} period – start date of RIXUBIS prophylaxis regimen on the i^{th} period + 1), where i=1,…,n is the number of periods where RIXUBIS treatment with prophylaxis was given before a bleeding episode, change of prophylaxis regimen, or end of study. The treatment duration for prophylaxis has been calculated for subjects that were on RIXUBIS prophylaxis treatment for at least 3 months.

ABR is defined as the number of unique bleeds during prophylaxis / (RIXUBIS treatment duration for prophylaxis/365.25).

Table 10: FIX Recovery at Baseline Visit (EFAS)

	Total (N=25)
Was FIX Recovery Test Conducted? [n (%)]	
Yes	25 (100)
No	0
Missing	0
FIX Concentration Value at Pre-infusion (IU/dL)	
n	25
Mean (SD)	2.08 (4.243)
Median	1.00
Q1, Q3	1.00, 1.00
Min, Max	1.0, 21.8
Missing	0
FIX Concentration Value at 30 min Post-infusion (IU/dL)	
n	22
Mean (SD)	46.98 (16.349)
Median	51.30
Q1, Q3	32.10, 61.40
Min, Max	17.3, 75.0
Missing	3
Body Weight for Calculation of the Incremental Recovery (kg)	
n	25
Mean (SD)	56.04 (12.041)
Median	53.60
Q1, Q3	47.60, 62.00
Min, Max	40.0, 88.1
Missing	0
Incremental Recovery [(IU/dL)/(IU/kg)][b]	
n	22
Mean (SD)	0.945 (0.2564)
Median	0.940
Q1, Q3	0.780, 1.150
Min, Max	0.43, 1.40
Missing	3
If On-demand regimen:	0

EFAS=Effectiveness Full Analysis Set; FIX=Recombinant Fact IX; IU=international unit; Max=Maximum; Min=Minimum; Q1=First Quartile; Q3=Third quartile; SD=Standard deviation
n = Number of subjects with available data.
N = Total number of subjects in the EFAS.
% = Percentage of subjects (n) based on subjects with available (non-missing) data within the EFAS.
[a] Percentages based on subjects who had infusion interrupted.
[b] Incremental Recovery [(IU/dL)/(IU/kg)] = [Post FIX (IU/dL) – Pre FIX (IU/dL)] / Weight adjusted Dose (IU/kg).

Safety results

Extent of Exposure

Out of 25 subjects, 23 subjects received RIXUBIS treatment for prophylaxis for at least 3 months. Mean (SD) of RIXUBIS treatment duration for prophylaxis was 179.5 (9.08) days. Mean (SD) of total number of infusions given for prophylaxis per subject was 45.1 (12.08). A total of 6 subjects received RIXUBIS treatment to treat bleeding. Mean (SD) duration of RIXUBIS treatment to treat bleeding was 1.8 (1.33) days and mean (SD) number of infusions of RIXUBIS treatment to treat bleeding per subject was 1.3 (0.52). No subject received RIXUBIS treatment to maintain hemostasis.

Table 11: RIXUBIS Exposure (SAS)

	Total (N=25)
Total Number of Infusions, per Subject	
n	25
Mean (SD)	45.4 (12.00)
Median	50.0
Q1, Q3	44.0, 52.0
Min, Max	8, 59
Missing	0
Subjects received RIXUBIS Treatment for Prophylaxis	25
RIXUBIS Treatment Duration for Prophylaxis (days)[a]	
n	23
Mean (SD)	179.5 (9.08)
Median	179.0
Q1, Q3	175.0, 183.0
Min, Max	166, 204
Missing	2
Total Number of Infusions Given for Prophylaxis, per Subject	
n	25
Mean (SD)	45.1 (12.08)
Median	50.0
Q1, Q3	42.0, 52.0
Min, Max	8, 59
Missing	0
Subjects received RIXUBIS Treatment to Treat Bleeding	6
RIXUBIS Treatment Duration to Treat Bleeding (days)[b]	
n	6
Mean (SD)	1.8 (1.33)
Median	1.0
Q1, Q3	1.0, 3.0
Min, Max	1, 4
Missing	0
Total Number of Infusions Given to Treat Bleeding, per Subject	
n	6
Mean (SD)	1.3 (0.52)
Median	1.0
Q1, Q3	1.0, 2.0
Min, Max	1, 2
Missing	0
Subjects received RIXUBIS Treatment to Maintain Hemostasis	0
RIXUBIS Treatment Duration to Maintain Hemostasis (days)[c]	
n	0
Mean (SD)	- (-)
Median	-
Q1, Q3	-, -
Min, Max	-, -
Missing	0
Total Number of Infusions Given to Maintain Hemostasis, per Subject	
n	0
Mean (SD)	- (-)
Median	-
Q1, Q3	-, -
Min, Max	-, -
Missing	0

Max=Maximum; Min=Minimum; Q1=First Quartile; Q3=Third quartile; SAS=Safety Analysis Set; SD=Standard deviation
n=Number of subjects with available data. N=Total number of subjects in the SAS

[a] RIXUBIS treatment duration for prophylaxis (days) = SUM (end date of RIXUBIS prophylaxis regimen on the i^{th} period – start date of RIXUBIS prophylaxis regimen on the i^{th} period + 1), where i= 1,…,n is the number of periods where RIXUBIS treatment with prophylaxis was given before a bleeding, change of prophylaxis regimen, or end of study. The treatment duration for prophylaxis has been calculated for subjects that were on RIXUBIS prophylaxis treatment for at least 3 months.

[b] RIXUBIS treatment duration to treat bleeding (days) =SUM (end date of RIXUBIS treatment to treat bleeding on the i^{th} period – start date of RIXUBIS treatment to treat bleeding on the i^{th} period + 1), where i= 1,…,n is the number of periods where RIXUBIS treatment to treat bleeding was given.

[c] RIXUBIS treatment duration to maintain hemostasis (days) = SUM (end date of RIXUBIS treatment to maintain hemostasis on the i^{th} period – start date of RIXUBIS treatment to maintain hemostasis on the i^{th} period +1)
where i= 1,…,n is the number of periods where RIXUBIS treatment to maintain hemostasis was given.

Adverse Events

Table 12: Overall Adverse Events and Treatment-Emergent Adverse Events by RIXUBIS Treatment Regimen (SAS)

Category	On-Demand (N=0) n (%) m	Prophylaxis (N=25) n (%) m	Total (N=25) n (%) m
Any AE	0 0	4 (16.0) 5	4 (16.0) 5
Any Serious AE	0 0	0 0	0 0
AEs Related to RIXUBIS	0 0	0 0	0 0
Serious AEs Related to RIXUBIS	0 0	0 0	0 0
AEs Leading to Discontinuation from Study	0 0	0 0	0 0
AEs Leading to Death	0 0	0 0	0 0
Any TEAE	0 0	3 (12.0) 3	3 (12.0) 3
Any Serious TEAE	0 0	0 0	0 0
TEAEs Related to RIXUBIS	0 0	0 0	0 0
Serious TEAEs Related to RIXUBIS	0 0	0 0	0 0
TEAEs Leading to Discontinuation from Study	0 0	0 0	0 0
TEAEs Leading to Death	0 0	0 0	0 0

AE=Adverse Event; SAS=Safety Analysis Set; TEAE=Treatment-emergent adverse event;
n = number of subjects experiencing the event; m = number of events.
N = number of subjects in the SAS and column.
% = Percentages are based on all enrolled subjects in the SAS within each column.
Subjects were counted once per category.
A treatment-emergent adverse event (TEAE) is defined as any event not presented prior to the initiation of RIXUBIS or any event already present that worsens in either intensity or frequency following exposure to RIXUBIS.

Table 13: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and RIXUBIS Treatment Regimen (SAS)

System Organ Class Preferred Term	On-Demand (N=0) n (%) m	Prophylaxis (N=25) n (%) m	Total (N=25) n (%) m
Any TEAE	0 0	3 (12.0) 3	3 (12.0) 3
Musculoskeletal and connective tissue disorders	0 0	2 (8.0) 2	2 (8.0) 2
Arthropathy	0 0	1 (4.0) 1	1 (4.0) 1
Joint swelling	0 0	1 (4.0) 1	1 (4.0) 1
Infections and infestations	0 0	1 (4.0) 1	1 (4.0) 1
Dengue fever	0 0	1 (4.0) 1	1 (4.0) 1

SAS=Safety Analysis Set; TEAE=Treatment-emergent adverse event
% = Percentages are based on all enrolled subjects in the SAS within each column.
n = number of subjects experiencing the event. m = number of events.
Adverse events were classified into system organ class and preferred term using version 24.0 of MedDRA.
Subjects were counted once per system organ class and once per preferred term.
A treatment-emergent adverse event (TEAE) is defined as any event not presented prior to the initiation of RIXUBIS or any event already present that worsens in either intensity or frequency following exposure to RIXUBIS.

Table 14: Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, Preferred Term and RIXUBIS Treatment Regimen (SAS)

System Organ Class Preferred Term	Severity	On-Demand (N=0) n (%)	Prophylaxis (N=25) n (%)	Total (N=25) n (%)
Any TEAE	Mild	0	1 (4.0)	1 (4.0)
	Moderate	0	1 (4.0)	1 (4.0)
	Severe	0	1 (4.0)	1 (4.0)
Musculoskeletal and connective tissue disorders	Mild	0	0	0
	Moderate	0	1 (4.0)	1 (4.0)
	Severe	0	1 (4.0)	1 (4.0)
Arthropathy	Mild	0	0	0
	Moderate	0	0	0
	Severe	0	1 (4.0)	1 (4.0)
Joint swelling	Mild	0	0	0
	Moderate	0	1 (4.0)	1 (4.0)
	Severe	0	0	0
Infections and infestations	Mild	0	1 (4.0)	1 (4.0)
	Moderate	0	0	0
	Severe	0	0	0
Dengue fever	Mild	0	1 (4.0)	1 (4.0)
	Moderate	0	0	0
	Severe	0	0	0

SAS=Safety Analysis Set; TEAE=Treatment-emergent adverse event
% = Percentages are based on all enrolled subjects in the Safety Analysis Set within each column.
n = number of subjects experiencing the event; N= total number of subjects.
Adverse events were classified into system organ class and preferred term using version 24.0 of MedDRA.
Subjects were counted once per system organ class and once per preferred term at the maximum severity.
A treatment-emergent adverse event (TEAE) is defined as any event not presented prior to the initiation of RIXUBIS or any event already present that worsens in either intensity or frequency following exposure to RIXUBIS.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no deaths, SAEs, discontinuations due to AEs or other significant AEs reported during the study.

Clinical Laboratory Evaluation

No subject reported clinically significant abnormal hematological, biochemistry, or urinalysis values at any visit.

Table 15: Shift from Baseline in Clinical Laboratory Results by RIXUBIS Treatment Regimen: Hematology (SAS)

	On-Demand (N=0)				Prophylaxis (N=25)			
	Baseline[a]				Baseline[a]			
Parameter Visit Category	Low n (%)	Normal n (%)	High n (%)	Total n (%)	Low n (%)	Normal n (%)	High n (%)	Total n (%)
Basophils (%)								
End of Treatment								
Low	0	0	0	0	0	0	0	0
Normal	0	0	0	0	0	21 (100)	0	21 (100)
High	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	21	0	21
Basophils Absolute (x10E9/L)								
End of Treatment								
Low	0	0	0	0	0	0	0	0
Normal	0	0	0	0	0	21 (100)	0	21 (100)
High	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	21	0	21
Eosinophils (%)								
End of Treatment								
Low	0	0	0	0	0	0	0	0
Normal	0	0	0	0	0	18 (90.0)	0	18 (85.7)
High	0	0	0	0	0	2 (10.0)	1 (100)	3 (14.3)
Total	0	0	0	0	0	20	1	21
Eosinophils Absolute (x10E9/L)								
End of Treatment								
Low	0	0	0	0	0	0	0	0
Normal	0	0	0	0	0	20 (100)	0	20 (95.2)
High	0	0	0	0	0	0	1 (100)	1 (4.8)
Total	0	0	0	0	0	20	1	21
Ery. Mean Corpuscular HGB Concentration (g/L)								
End of Treatment								
Low	0	0	0	0	3 (75.0)	1 (5.9)	0	4 (19.0)
Normal	0	0	0	0	1 (25.0)	16 (94.1)	0	17 (81.0)
High	0	0	0	0	0	0	0	0
Total	0	0	0	0	4	17	0	21
Ery. Mean Corpuscular Volume (fL)								
End of Treatment								
Low	0	0	0	0	2 (100)	2 (11.8)	0	4 (19.0)
Normal	0	0	0	0	0	15 (88.2)	0	15 (71.4)
High	0	0	0	0	0	0	2 (100)	2 (9.5)
Total	0	0	0	0	2	17	2	21

Erythrocytes (x10E12/L)								
End of Treatment								
Low	0	0	0	0	0	0	0	0
Normal	0	0	0	0	0	20 (100)	0	20 (95.2)
High	0	0	0	0	0	0	1 (100)	1 (4.8)
Total	0	0	0	0	0	20	1	21
Hematocrit (V/V)								
End of Treatment								
Low	0	0	0	0	0	2 (11.1)	0	2 (9.5)
Normal	0	0	0	0	3 (100)	16 (88.9)	0	19 (90.5)
High	0	0	0	0	0	0	0	0
Total	0	0	0	0	3	18	0	21
Hemoglobin (g/L)								
End of Treatment								
Low	0	0	0	0	4 (66.7)	1 (6.7)	0	5 (23.8)
Normal	0	0	0	0	2 (33.3)	14 (93.3)	0	16 (76.2)
High	0	0	0	0	0	0	0	0
Total	0	0	0	0	6	15	0	21
Leukocytes (x10E9/L)								
End of Treatment								
Low	0	0	0	0	1 (100)	0	0	1 (4.8)
Normal	0	0	0	0	0	19 (100)	1 (100)	20 (95.2)
High	0	0	0	0	0	0	0	0
Total	0	0	0	0	1	19	1	21
Lymphocytes (%)								
End of Treatment								
Low	0	0	0	0	0	0	0	0
Normal	0	0	0	0	0	20 (100)	0	20 (95.2)
High	0	0	0	0	0	0	1 (100)	1 (4.8)
Total	0	0	0	0	0	20	1	21
Lymphocytes Absolute (x10E9/L)								
End of Treatment								
Low	0	0	0	0	1 (100)	0	0	1 (4.8)
Normal	0	0	0	0	0	19 (100)	1 (100)	20 (95.2)
High	0	0	0	0	0	0	0	0
Total	0	0	0	0	1	19	1	21

Monocytes (%)								
End of Treatment								
Low	0	0	0	0	1 (16.7)	3 (20.0)	0	4 (19.0)
Normal	0	0	0	0	5 (83.3)	12 (80.0)	0	17 (81.0)
High	0	0	0	0	0	0	0	0
Total	0	0	0	0	6	15	0	21
Monocytes Absolute (x10E9/L)								
End of Treatment								
Low	0	0	0	0	1 (20.0)	2 (12.5)	0	3 (14.3)
Normal	0	0	0	0	4 (80.0)	14 (87.5)	0	18 (85.7)
High	0	0	0	0	0	0	0	0
Total	0	0	0	0	5	16	0	21
Neutrophils (%)								
End of Treatment								
Low	0	0	0	0	0	0	0	0
Normal	0	0	0	0	1 (100)	18 (94.7)	1 (100)	20 (95.2)
High	0	0	0	0	0	1 (5.3)	0	1 (4.8)
Total	0	0	0	0	1	19	1	21
Neutrophils Absolute (x10E9/L)								
End of Treatment								
Low	0	0	0	0	1 (100)	0	0	1 (4.8)
Normal	0	0	0	0	0	19 (95.0)	0	19 (90.5)
High	0	0	0	0	0	1 (5.0)	0	1 (4.8)
Total	0	0	0	0	1	20	0	21
Platelets (x10E9/L)								
End of Treatment								
Low	0	0	0	0	0	0	0	0
Normal	0	0	0	0	1 (100)	16 (100)	1 (100)	18 (100)
High	0	0	0	0	0	0	0	0
Total	0	0	0	0	1	16	1	18

ery=erythrocyte; n=number of subjects in each category; N=number of subjects in the SAS and column; SAS=Safety Analysis Set

%: Percentages are based on the total number of subjects in the given category at baseline in the SAS within each column.

*Baseline is defined as last assessment prior to first dose.

Table 16: Shift from Baseline in Clinical Laboratory Results by RIXUBIS Treatment Regimen: Biochemistry (SAS)

	On-Demand (N=0) Baseline*				Prophylaxis (N=25) Baseline*			
Parameter Visit Category	Low n (%)	Normal n (%)	High n (%)	Total n (%)	Low n (%)	Normal n (%)	High n (%)	Total n (%)
Alanine Aminotransferase (U/L)								
End of Treatment								
Low	0	0	0	0	0	0	0	0
Normal	0	0	0	0	0	19 (90.5)	0	19 (86.4)
High	0	0	0	0	0	2 (9.5)	1 (100)	3 (13.6)
Total	0	0	0	0	0	21	1	22
Albumin (g/L)								
End of Treatment								
Low	0	0	0	0	0	0	0	0
Normal	0	0	0	0	0	19 (95.0)	2 (100)	21 (95.5)
High	0	0	0	0	0	1 (5.0)	0	1 (4.5)
Total	0	0	0	0	0	20	2	22
Albumin/Total Protein (g/L)								
End of Treatment								
Low	0	0	0	0	0	0	0	0
Normal	0	0	0	0	0	14 (87.5)	6 (100)	20 (90.9)
High	0	0	0	0	0	2 (12.5)	0	2 (9.1)
Total	0	0	0	0	0	16	6	22
Alkaline Phosphatase (IU/L)								
End of Treatment								

Parameter Visit Category	Low n (%)	Normal n (%)	High n (%)	Total n (%)	Low n (%)	Normal n (%)	High n (%)	Total n (%)
Low	0	0	0	0	0	0	0	0
Normal	0	0	0	0	0	19 (95.0)	0	19 (86.4)
High	0	0	0	0	0	1 (5.0)	2 (100)	3 (13.6)
Total	0	0	0	0	0	20	2	22
Aspartate Aminotransferase (U/L)								
End of Treatment								
Low	0	0	0	0	0	0	0	0
Normal	0	0	0	0	0	20 (90.9)	0	20 (90.9)
High	0	0	0	0	0	2 (9.1)	0	2 (9.1)
Total	0	0	0	0	0	22	0	22
Bicarbonate (mmol/L)								
End of Treatment								
Low	0	0	0	0	1 (50.0)	1 (5.0)	0	2 (9.1)
Normal	0	0	0	0	1 (50.0)	19 (95.0)	0	20 (90.9)
High	0	0	0	0	0	0	0	0
Total	0	0	0	0	2	20	0	22

n=number of subjects in each category; N=number of subjects in the SAS and column; SAS=Safety Analysis Set
% = Percentages are based on the total number of subjects in the given category at baseline in the Safety Analysis Set within each column.
* Baseline is defined as last assessment prior to first dose.

Immunogenicity

Table 17: Summary of Positive Immunogenicity Results

Parameter Visit	On-Demand (N=0)		Prophylaxis (N=25)		Total (N=25)	
	N (i)	n (%)	N (i)	n (%)	N (i)	n (%)
Binding Antibodies to FIX						
Screening	0	0	25	0	25	0
Baseline	0	0	25	0	25	0
Visit 1	0	0	23	0	23	0
Visit 2	0	0	21	0	21	0
End of Treatment	0	0	22	1 (4.5)	22	1 (4.5)
Binding Antibodies to CHO						
Screening	0	0	25	0	25	0
Baseline	0	0	25	0	25	0
Visit 1	0	0	23	0	23	0
Visit 2	0	0	21	0	21	0
End of Treatment	0	0	22	0	22	0
Binding Antibodies to rFurin						
Screening	0	0	25	0	25	0
Baseline	0	0	25	0	25	0
Visit 1	0	0	23	0	23	0
Visit 2	0	0	21	0	21	0
End of Treatment	0	0	22	0	22	0
FIX Nijmegen						
Screening	0	0	25	0	25	0
Baseline	0	0	25	0	25	0
Visit 1	0	0	23	0	23	0
Visit 2	0	0	19	0	19	0
End of Treatment	0	0	22	0	22	0

BU=Bethesda Unit; CHO=Chinese Hamster Ovary. FIX=recombinant factor IX; IgG=Immunoglobulin G; IgM=Immunoglobulin M; SAS=Safety Analysis Set
n = number of subjects who had at least 1 positive result at a given visit.
N = Total number of subjects in the SAS and column. N(i) = Number of subjects in the SAS who had immunogenicity clinical laboratory assessments in the specified analysis window and column. % = Percentage of subjects who had a positive result, based on N(i) as denominator.
A positive result is defined as any detectable level.
For FIX Nijmegen, negative result is defined as any value <0.6 BU.

Vital Signs

The mean (SD) values for diastolic blood pressure, systolic blood pressure, pulse rate, respiratory rates, and temperature at EOT were comparable to those observed at baseline.

Postmarketing Safety Experience

RIXUBIS has been approved for the treatment and prevention of bleeding episodes in patients with hemophilia B (congenital FIX deficiency), routine prophylaxis of bleeding episodes in patients with hemophilia B, and perioperative management of bleeding in patients with hemophilia B in 21 countries/regions (approved via centralized procedure in the EU) as of 30 Jun 2022. In India, initial approval of RIXUBIS was granted to Baxter India Pvt. Ltd. on 19 Jan 2015. Approval was then transferred and reissued to Baxalta Bioscience India Pvt. Ltd. on 21 Mar 2016.

Cumulatively from 01 Oct 2013 to 30 Jun 2022, approximately 10,696,000 IU of RIXUBIS were sold in India with an estimated 3,056 patient treatments (mean of 5 patients/year) on prophylaxis and estimated 2,453 patient treatments (mean of 19 patients/year) on-demand therapies. From 01 Jul 2021 to 30 Jun 2022, approximately 7,327,750 IU of RIXUBIS were sold in India with an estimated 2,094 patient treatments (20 patients/year) on prophylaxis and estimated 1,680 patient treatments (84 patients/year) on-demand therapies.

Study 251602 was a Phase 4, multicenter, prospective, interventional, postmarketing study in hemophilia B PTPs in India receiving RIXUBIS under standard clinical practice. The safety results of this study suggest that RIXUBIS is safe in hemophilia B PTPs treated under standard clinical practice in India. Results from this study are consistent with previous real-world evidence in a South Korean population (Choi et al. 2020) and Phase 1/3 clinical trial (Windyga et al. 2014). The total of 23/25 prophylaxis subjects in India who completed the study provides sufficient evidence for safety and efficacy of RIXUBIS in hemophilia B PTPs treated under standard clinical practice in India. The results of Study 261502 did not impact the benefit-risk profile of RIXUBIS.

Postmarketing Safety Surveillance Planning and Risk Management

RIXUBIS has been shown to be efficacious for routine prophylactic treatment and control of bleeding episodes (on-demand treatment) in PTPs in adults and pediatrics with severe or moderately severe hemophilia B. RIXUBIS has also been shown to be efficacious in surgical hemostasis in adult patients with hemophilia B.

RIXUBIS is generally well tolerated. Important identified risks include hypersensitivity reactions (including reactions/antibodies to CHO protein). Important potential risks include inhibitor formation, lack of effect, thromboembolic events (eg, disseminated intravascular coagulation and fibrinolysis), and nephrotic syndrome following attempted immune tolerance induction in hemophilia B patients with FIX inhibitors and a history of allergic reactions. These risks continue to be monitored as a part of routine pharmacovigilance activities, and detailed AE information on reports of inhibitor formation are collected via a FIX inhibitor AE questionnaire.

2.3.3. Discussion on clinical aspects

The MAH submitted the clinical study report of study 251602, as required in Article 46 of Regulation (EC) No 1901/2006 due to the inclusion of paediatric subjects, while acknowledging the failure to do so within the specified time frame of six months after completion of last subject (Study Completed: 11 Aug 2021; Date of the Report: 27 Jul 2022). Upon request the Applicant clarified that the delayed submission was due to insufficient detail in the internal procedure for handling the requirements of Article 46 submissions and that actions are in place to prevent future submissions to be delayed. The explanation is acknowledged, but the delayed submission is critically noted.

Trial 251602 was a single-arm, open-label, phase IV, multi-centre, prospective, interventional, post-marketing study in haemophilia B patients in India receiving Rixubis as on-demand or prophylaxis under standard clinical practice. The duration of the study was 36 months from enrolment of the first subject, to study completion of the last subject on 11th of August 2021. In total, 25 subjects were planned and enrolled, of which 23 completed the study. Reasons for the two study discontinuations can be followed (one each for non compliance with study protocol and due to criminal record). All 25 patients were included in the effectiveness full analysis set (EFAS) and safety analysis set (SAS). The mean (SD) age of included patients was 24.6 (8.29) years, 5 patients were between 12 to 18 years old. All subjects received Rixubis in the prophylactic setting for a total duration of three months after enrolment. No concerns derive from the two protocol amendments and reported protocol deviations (vast majority related to IP compliance).

The primary outcome was number of possibly or probably related SAEs (including FIX inhibitors) and number and percentage of subjects with possibly or probably related SAEs (including FIX inhibitors) during or after first Rixubis infusion. SAEs and AEs were summarized by system organ class SOC) and

preferred term (PT). Efficacy was established by analysis of annualized bleeding rate (ABR) with prophylactic use of Rixubis, in subjects on prophylaxis treatment of at least 3 months. The choice of study objectives and corresponding endpoints is appropriate.

An Erratum for the study report of study 251602 was also submitted, which clarified one correction for an erroneously depicted valued of the ABR SD in the body text of the CSR. No concern arises from this Erratum.

Conclusion on efficacy

Incremental recovery

The mean IR at baseline was 0.945 (SD: 0.2564) (IU/dL)/(IU/kg) with a minimum value of 0.43 (IU/dL)/(IU/kg) in 22 subjects, which is comparable to the rate reported in the EPAR of Rixubis with 0.79 (SD: 0.2) (IU/dL)/(IU/kg) and a minimum of 0.26 (IU/dL)/(IU/kg) at the first exposure day (as determined for all subjects in the combined phase 1/3 study250901).

Consumption

The mean total number of infusions given for prophylaxis per subject (45.1, SD:12.08) during the mean treatment duration of 179.5 (SD: 9.08) days in study 251602 is in line with the recommended interval for infusions in patients ≥12 years during prophylactic treatment as recommended in the product information (i.e. 3-4 days).

Treatment of bleeding episodes

The mean duration of Rixubis treatment to treat bleeding episodes was 1.8 (SD: 1.33) days with a maximum of 4 days and the mean number of infusions of Rixubis treatment to treat bleeding episodes per subject was 1.3 (SD: 0.52) with a maximum of 2 infusions (i.e. all with good or excellent treatment success; n=6 subjects received additional Rixubis for bleeding episodes). No subject received RIXUBIS treatment to maintain haemostasis. No concerns derive from the treatment of bleeding episodes in study 251602.

Unique bleeding episodes

Out of 25 subjects enrolled in prophylactic Rixubis treatment group, 8 subjects (32%) experienced a total of 13 unique bleeding episodes during the study and 3 of these unique bleeding episodes occurred prior to starting prophylactic treatment. While most bleeding episodes after start of treatment only occurred once in each patient, one subject experienced 3 unique bleeding episodes and two further subjects had 2 unique bleeding episodes each. No subject developed a new target joint (i.e. ≥4 bleeds within 6 months) for the treatment duration of 3 months. The vast majority of bleeds were spontaneous (at least n=11 as the two remaining bleeds are of unknown cause) and mild (n=3, rest was moderate) joint (n=12) bleeds (see below the discussion on ABR for joint and spontaneous bleeds). No traumatic bleeds are reported. Overall, the unique bleeding episodes reported are within the expected range and raise no further concerns.

Annualized bleeding Rate

The mean ABR for prophylactic use of Rixubis was 0.914 (SD: 1.6896), with highest ABR for joints of 0.82 (SD: 1.557). The mean ABR for spontaneous bleeding episodes during RIXUBIS prophylaxis was 0.74 (SD: 1.668). The mean ABR for minor severity and moderate severity during RIXUBIS prophylaxis were 0.45 (SD: 0.869) and 0.47 (SD: 1.463), respectively. The median ABR in all mentioned categories was 0. This is in line with ABR reported in similar trials and no concerns are raised.

Conclusion on safety

All enrolled subjects who received Rixubis at any time during the trial (n=25) were included in the safety analysis set. Out of 25 subjects, 23 received Rixubis treatment for prophylaxis for at least 3 months, with a mean duration of 179.5 (SD 9.08) days. No deaths, SAEs or other significant AEs were reported during the study. 3 subjects experienced TEAEs, all of them occurring once: arthropathy (severe), joint swelling (moderate) and Dengue fever (mild). Two further AEs were not considered treatment emergent as they occurred before IMP administration. All events were considered not to be related to the investigational product by the investigator. The moderate event of joint swelling was also rated as bleeding event of the left elbow in a subject with in total 3 bleeding episodes (also Conclusion on efficacy above), whereas the event of arthropathy was not caused by a bleeding event. Importantly, no new or unexpected safety finding was observed in study 251602.

Binding antibodies to FIX were found in only 1 subject at EOT Visit and the titre value for the binding antibodies to FIX was 1/160. No antibodies to rFurin or CHO were detected in any subject over the course of the trial. Importantly, also no inhibitory antibodies against FIX were identified throughout the study.

3. Rapporteur's overall conclusion and recommendation

No concerns derive from data reported from trial 251602 regarding the current B/R for Rixubis Efficacy and safety results did not reveal any unexpected findings and appear to be in line with results from previous studies. Also, no changes of the PI appear required. However, the delayed submission beyond 6 months after study completion is critically noted.

☒ **Fulfilled:**

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The Applicant is asked to clarify reasons for the delayed submission of the study report for Study 251602.

The timetable is a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

Question 1:

The Applicant is asked to clarify reasons for the delayed submission of the study report for Study 251602.

MAH Response:

The reason for the delay was due to insufficient detail in the internal procedure for handling the requirements of Article 46 of the Paediatric Regulation EC 1901/2006. Takeda is now proactively monitoring upcoming studies that include paediatric patients to support timely submission of CSRs per the Article 46 timelines.

Corrective actions are in process. Preventative measures have been put in place to strengthen internal processes, to train relevant stakeholders in the organisation on paediatric requirements, and to monitor studies in scope of Article 46.

Rapporteur's assessment and conclusion:

The Applicant clarified that the delayed submission was due to insufficient detail in the internal procedure for handling the requirements of Article 46 submissions and that actions are in place to prevent future submissions to be delayed.

Issue resolved.