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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Rixubis

nonacog gamma

Procedure no: EMEA/H/C/003771/P46/005

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Introduction

On the 12th of April, 2018, the MAH submitted a completed study for RIXUBIS (Nonacog gamma B02BD04) which also includes a paediatric subset, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

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

A final study report and an updated Clinical Overview have been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study 251001 "*BAX326 (Recombinant Factor IX): Evaluation of Safety, Immunogenicity, and Hemostatic Efficacy in Previously Treated Patients with Severe (FIX level < 1%) or Moderately Severe (FIX level 1-2%) Hemophilia B – A Continuation Study*" is part of a clinical development program. As per the "Guideline on clinical investigation of recombinant and human plasma-derived factor IX products" (EMA/CHMP/BPWP/144552/2009 Rev. 1), 50 previously treated patients (PTPs) need to be followed up to a total of 100 exposure days in the context of the clinical development plan for these kind of products within 4 years after obtaining the marketing authorisation as a post-approval measure. This requirement was also reflected in the PIP.

2.2. Information on the pharmaceutical formulation used in the study

BAX326 is a purified protein produced by recombinant DNA technology. BAX326 is not derived from human blood or plasma products, and its manufacture does not include animal or human components. BAX326 contains no preservatives. Recombinant factor IX is secreted by a Chinese Hamster Ovary (CHO) cell line into a defined cell culture medium that does not contain any proteins derived from animal or human sources as well as hormones, and the recombinant factor IX is purified by a chromatography purification process that does not require a monoclonal antibody step.

The process includes validated virus inactivation/removal steps, namely solvent/detergent treatment and 15 nm nanofiltration. The S/D treatment has the ability to inactivate lipid-enveloped viruses, whereas the nanofiltration step has the ability to remove both lipid-enveloped and non-lipid-enveloped viruses. BAX326 is predominantly a single component by SDS-polyacrylamide gel electrophoresis evaluation. BAX326 has structural and functional characteristics comparable to those of endogenous FIX. Furthermore, studies demonstrate that the structure, identity, purity, potency, and functional integrity of BAX326 are comparable to those of a commercial rFIX. The polypeptide sequence of BAX326 is identical to that of a commercial rFIX and the post-translational modifications are comparable. The purity and specific activity (in units of clotting activity per mg of total protein) of BAX326 are within the same range as that found for a commercial rFIX.

BAX326 is formulated as a sterile, nonpyrogenic, lyophilized powder preparation, intended for intravenous (IV) infusion. It is available in single-use vials containing the labelled amount of factor IX activity, expressed in International Units (IU). Each vial contains nominally 250, 500, 1000, 2000, or 3000 IU of coagulation factor IX (recombinant).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study number 251001: "*BAX326 (Recombinant Factor IX): Evaluation of Safety, Immunogenicity, and Hemostatic Efficacy in Previously Treated Patients with Severe (FIX level < 1%) or Moderately Severe (FIX level 1-2%) Hemophilia B – A Continuation Study*"

2.3.2. Clinical study

The MAH submitted a final report for Study 251001:

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

Description

This was a phase 3 study conducted in PTPs with severe (FIX level <1%) or moderately severe (FIX level 1-2%) hemophilia B who had completed the phase 1/3 BAX326 pivotal protocol 250901 or the phase 2/3 BAX326 pediatric protocol 251101 or were newly recruited, BAX326 naïve subjects.

Methods

Objectives

Primary Objective

- To further evaluate safety of BAX326 in terms of investigational product (IP)-related AEs as well as clinically significant changes in routine laboratory parameters (hematology/clinical chemistry) and vital signs

Secondary objectives:

- To further evaluate the hemostatic efficacy of BAX326 in the prevention and routine prophylaxis of acute bleeding episodes using various dose regimens
- To further evaluate the hemostatic efficacy of BAX326 in the management of acute bleeding episodes
- To further evaluate the immunogenicity of BAX326 for up to 100 EDs to BAX326viii
- To monitor incremental recovery (IR) of BAX326 over time
- To evaluate changes in HR QoL, Patient Activity Level and health resource use

Tertiary/Exploratory Objective:

- Exploratory: To correlate pre-infusion thrombin generation assay (TGA) parameters with pre-infusion FIX levels and spontaneous breakthrough bleeds in a subset of subjects receiving twice weekly standard or modified prophylaxis including PK-tailored prophylaxis

Study design

This study was designed as a prospective, open-label, multicentre, uncontrolled, phase 3 study in approximately 100 PTPs with severe (FIX level < 1%) or moderately severe (FIX level 1-2%)

hemophilia B, who had completed the pivotal phase 1/3 Protocol 250901 or the pediatric phase 2/3 Protocol 251101 (Cohort 1), as well as in approximately 25 BAX326 naïve subjects (Cohort 2).

Study population /Sample size

The sample size was not based on statistical consideration. It was determined by the number of subjects treated under the BAX326 pivotal protocol 250901 and the pediatric protocol 251101, who were willing to participate in this study and met the eligibility criteria, as well as by regulatory requirements (enrolment of 25 BAX326 naïve subjects).

A total of 117 subjects were enrolled. Of these, 65 had transitioned from BAX326 Pivotal Study 250901, 20 from BAX326 Pediatric Study 251101, and 32 were newly recruited, BAX326 naïve subjects.
Of 117 enrolled subjects, 115 received treatment with investigational product (IP). All 85 subjects who had transitioned from the pivotal/pediatric studies (Cohort 1) continued to receive IP in this study. Of the 32 newly recruited, BAX326 naïve subjects (Cohort 2), 30 received treatment with IP. The 85 subjects who had transitioned from the BAX326 pivotal and pediatric studies had a mean of 49.7 (±15.47) (median: 52.0, range: 5.0-83.0) prior EDs to BAX326 when they entered this continuation study.
Subjects transitioning from Pivotal Study 250901 or Pediatric Study 251101 had the option of receiving prophylactic or on-demand treatment. Newly recruited subjects could only receive prophylactic treatment.

The following table gives an overview over the age groups included in the FAS (Full Analysis Set)

Table 2. Number of Subjects in FAS (n=115) per Age Group

Age group 1	
<12 years	21
≥12 years	94
Age group 2	
<6 years	8
≥6 to <12 years	13
≥12 to <18 years	5
≥18 years	89

Source: CSR 251001 Table 21, Table 24

As can be seen from the table above, most subjects were ≥18 years of age (n=89)

Treatments

Lyophilized powder and solvent for solution for injection. The IP was applied twice weekly, or tailored to the individual needs of subjects as determined by the investigator (modified prophylaxis), or PK-tailored, or on-demand.
One dose (75 ± 5 IU/kg) was to be given at each of the study visits to assess IR.

Treatment with BAX326 was at the discretion of the investigator. Subjects transitioning from Pivotal Study 250901 or Pediatric Study 251101 had the option of receiving prophylactic or on-demand treatment. Newly recruited subjects could only receive prophylactic treatment. Bleeding episodes were also to be treated with BAX326.

- The following prophylactic treatment options were available:
  - Standard prophylactic regimen at a dose of 50 IU/kg, ranging from 40-60 IU/kg, which could be increased up to 75 IU/kg, if applicable, for subjects ≥ 12 years. The dose range for pediatric PTPs < 12 years was 40-80 IU/kg.
  - Modified prophylaxis as determined by the investigator. The dose could be increased up to 100 IU/kg, if applicable.
  - PK-tailored prophylactic administration of BAX326 based on subject's individual PK. The maximum dose was 120 IU/kg.
  - On-demand treatment only: The dose to be used for on-demand treatment depended on the severity of the bleed. (This treatment option was not applicable for newly recruited subjects.)
- 75 ± 5 IU/kg at each regular visit to assess IR.
- Individual subject treatment and dosing for IR during the optional additional visits for subjects under standard or modified prophylaxis.

A total of 110 subjects received overall prophylaxis. This includes 108 subjects on standard prophylaxis, 26 on modified prophylaxis, and 3 on PK-tailored prophylaxis. Thirteen subjects received on-demand treatment.

Outcomes/endpoints

The primary outcome measure in this study was AEs possibly or probably related to BAX326.

Safety

Primary Safety Outcome:	- Adverse events possibly or probably related to IP
Secondary Safety Outcome:	- Development of inhibitory and total binding antibodies to FIX - Development of antibodies to CHO proteins and rFurin - Occurrence of severe allergic reactions, e.g. anaphylaxis - Occurrence of thrombotic events - Clinically significant changes in routine laboratory parameters (hematology and clinical chemistry) and vital signs

Efficacy

Secondary Efficacy Outcomes:	- Treatment of bleeding episodes: number of infusions per bleeding episode, overall hemostatic efficacy rating at resolution of bleed
	- Prophylaxis: annualized bleeding rate (ABR)
	- Consumption of BAX326:
	  - Number of infusions and weight-adjusted consumption per month and per year
	  - Weight-adjusted consumption per event (prophylaxis and on-demand)

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

Health Related Quality of Life, Patient Activity Level and Pharmacoeconomic Parameters:

For subjects 2 to 7 years:	- Generic: PedsQL™ (Parent-proxy versions: age group 2-4 years and age group 5-7 years) - Health resource use (hospitalizations, emergency room visits, doctor office visits, etc.) - Patient Activity Level
For subjects 8 to 11 years:	- Disease-specific: Haemo-QoL, short version - Generic: PedsQL™ Child version - Health resource use (hospitalizations, emergency room visits, doctor office visits, etc.) - Patient Activity Level
For subjects 12 and 16 years:	- Disease-specific: Haemo-QoL short version - Generic: PedsQL™ - Health utility: EQ-5D - General pain assessment through a visual analog scale (VAS) - Health resource use - Patient Activity Level
For subjects aged 17 years:	- Disease-specific: Haem-A-QoL - Generic: SF-36 - Health Utility: EQ-5D - General pain assessment through a visual analog scale (VAS) - Health resource use - Patient Activity Level
Exploratory Outcome Measure:	- TGA parameters over 72 hours during PK (lag time, time to peak thrombin generation, peak thrombin generation, endogenous thrombin potential [ETP]) - TGA parameters pre- and post-infusion concurrent with IR determination for FIX and at some selected timepoints during prophylactic treatment

Statistical Methods

Safety, efficacy, PK, HRQoL and immunogenicity data from the additional BAX326 naïve subjects (Cohort 2) will be analyzed together with the data from the previously treated subjects (Cohort 1). In general, all efficacy, safety, PK, HRQoL and immunogenicity variables will be summarized using descriptive statistics. Continuous variables will be summarized by sample size [n], mean, standard deviation [SD], median, minimum, maximum, Q1 and Q3. Categorical variables will be summarized in frequency tables (n, frequencies, and percentages).

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

Results

Recruitment / Number analysed

The following table gives an overview of the subject distribution by age group in the FAS

In-text Table 2
Number of Subjects in FAS by Age Group Per Treatment Regimen

Age Group (Years)	Standard Prophylaxis	Modified Prophylaxis	PK-tailored prophylaxis	Overall Prophylaxis	On-demand
<6 (n=8)	8	1	0	8	0
≥6 - <12 (n=13)	13	4	0	13	0
≥12 - <18 (n=5)	5	2	0	5	0
≥18 (n=89)	82	19	3	84	13
Total (n=115)	108	26	3	110*	13

* Please note that the total number of subjects on overall prophylaxis is not the total of subjects per prophylactic treatment regimen. If a subject changed the treatment regimen during the study, the subject appears in all respective prophylactic treatment regimens but only once in overall prophylaxis.
Source: Table 12

Table 1
Subject Disposition
(Study 251001: All Subjects)

	Transitioning Subjects (Cohort 1)		Newly Recruited Subjects (Cohort 2)	
Category	Pivotal Study (250901) N (%)	Pediatric Study (251101) N (%)	N (%)	Overall N (%)
Enrolled Subjects (i.e. subjects who signed the informed consent)	65 (100.0)	20 (100.0)	32 (100.0)	117 (100.0)
Subjects Treated with IP[a]	65 (100.0)	20 (100.0)	30 (93.8)	115 (98.3)
Subjects Discontinued Study	15 (23.1)	2 (10.0)	4 (12.5)	21 (17.9)
Subjects Completed Study	50 (76.9)	18 (90.0)	28 (87.5)	96 (82.1)

[a] IP...Investigational Product

A total of 117 subjects were enrolled. Of these, 65 had transitioned from BAX326 Pivotal Study 250901, 20 from BAX326 Pediatric Study 251101, and 32 were newly recruited, BAX326 naïve subjects.

Of 117 enrolled subjects, 115 received treatment with investigational product (IP). All 85 subjects who had transitioned from the pivotal/pediatric studies (Cohort 1) continued to receive IP in this study. Of the 32 newly recruited, BAX326 naïve subjects (Cohort 2), 30 received treatment with IP. The 85 subjects who had transitioned from the BAX326 pivotal and pediatric studies had a mean of 49.7 (±15.47) (median: 52.0, range: 5.0-83.0) prior EDs to BAX326 when they entered this continuation study.

Subjects transitioning from Pivotal Study 250901 or Pediatric Study 251101 had the option of receiving prophylactic or on-demand treatment. Newly recruited subjects could only receive prophylactic treatment.

Of 96 enrolled subjects ≥12 years of age, the majority, ie, 91 subjects, were in the ≥18-year age group; 5 were in the age group ≥12 to <18 years. Of 21 enrolled subjects <12 years of age, 13 were in the age group ≥6 to <12 years and 8 in the <6-year age group.

All 8 subjects enrolled in the <6-year age group received treatment with IP; 7 of these subjects had transitioned from the pediatric study, 1 was a newly recruited subject. Seven subjects completed the study. One subject (who had transitioned from the pediatric study) discontinued.

All 13 subjects in the age group ≥6 to <12 years and all 5 subjects in the age group ≥12 to <18 years received treatment with IP. In both age groups, one subject discontinued, while all others (ie, 12 and 4 subjects, respectively) completed the study.

Of 91 subjects enrolled in the ≥18-year age group, 63 had transitioned from the pivotal study (Cohort 1) and 28 were newly recruited subjects (Cohort 2). All 63 subjects in Cohort 1 and 26 subjects in Cohort 2 received treatment with IP. There were 73 completers in this age group (49 in Cohort 1, 24 in Cohort 2); 18 subjects discontinued the study.

Baseline data

All 115 subjects in the FAS were male. The majority (ie, 99 subjects; 86.1%) were white, 10 subjects (8.7%) were Asian and one subject (0.9%) was Black/African American. For 5 subjects (4.3%) the race category “other” was reported.

In the FAS (n=115), the mean (± standard deviation (SD)) subject age was 29.6 (± 16.39) years (median: 28 years, range: 2-70 years). The mean (± SD) subject weight at screening was 63.37 (± 22.270) kg (median: 65 kg, range: 11.8-101.0 kg). In the PKFAS (n=6), the mean (± SD) subject age was 38.5 (± 12.77) years (median: 35.0 years, range: 22-57 years). The mean (± SD) subject weight at screening was 77.87 (± 14.41) kg (median: 81.15 kg, range: 51.9-92.0 kg)

The baseline FIX activity level for the 30 newly recruited subjects (Cohort 2) in the FAS was <1% in 23 subjects and 1-2% in 7 subjects. The FIX antigen levels in these 30 subjects was as follows: <1% in 5 subjects, 1-2% in 5 subjects, >2-5% in 3 subjects, >5-<40% in 7 subjects, ≥40% in 10 subjects.

Most subjects did not have target joints at screening (ie, 71 subjects, 61.7%). Of the 44 subjects who had target joints at screening, 25 (21.7%) had 1-2 target joints, 12 (10.4%) had 3-4 target joints, and 7 (6.1%) had >4 target joints.

Efficacy results

In continuation study 251001, the hemostatic efficacy of BAX326 for long-term prophylaxis (≥ 100 EDs) was further investigated by using various prophylactic treatment regimens. Subjects who had participated in pivotal study 250901 and pediatric study 251101 were enrolled in the continuation study as well as BAX326 naïve subjects (ie, not previously exposed to BAX326).

Annualized Bleeding Rate

For the analysis of ABR during prophylaxis, only subjects with an observation period of at least 3 months with BAX326 on the specified prophylactic treatment were included.

This includes 108 subjects on overall prophylaxis (106 subjects on standard prophylaxis, 22 subjects on modified prophylaxis, 2 subjects on PK-tailored prophylaxis). In addition, the ABR was analyzed for 13 subjects on on-demand treatment.

As expected, the ABR was considerably lower during prophylactic treatment than during on-demand treatment. While the median ABR was 16.5 (mean: 18.2 [± 11.17]) in the ondemand group (n=13), it was only 1.3 (mean: 3.3 [± 6.67] in the overall prophylaxis group (n=108).

ABR by treatment Regimen

By type of prophylactic treatment, the median and mean ABRs were as shown in the following table:

Table 11. Annualized Bleeding Rate (FAS)

Treatment	N	Median	Mean ABR	SD	Range
Standard prophylaxis	106	1.3	3.6	8.72	0.0-78.7
Modified prophylaxis	22	1.4	5.9	9.79	0.0-34.6
PK-tailored prophylaxis	2	1.9	1.9	1.96	0.5-3.3
Overall prophylaxis	108	1.3	3.3	6.67	0.0-52.2
On-demand treatment	13	16.5	18.2	11.17	0.0-31.1

Source: CSR 251001 Table 66

ABR by Age Group and Treatment Regimen

In the **<12-year age group (n=21)**, where all 21 subjects received standard prophylaxis and 5 also received modified prophylaxis, the median and mean ABRs for the two prophylactic regimens were comparable

Table 12. Annualized Bleeding Rate (FAS) – Age Group <12 Years (n=21)

Treatment	N	Median	Mean ABR	SD	Range
Standard prophylaxis	21	0.9	1.2	1.37	0.0-4.2
Modified prophylaxis	5	0.6	1.0	1.22	0.0-2.9

Source: CSR 251001 Table 68

In the **<6-year age group (n=8)**, where all 8 subjects received standard prophylaxis and one subject also received modified prophylaxis, the median and mean ABRs were as shown in the following table

Table 13. Annualized Bleeding Rate (FAS) – Age Group <6 Years (n=8)

Treatment	N	Median	Mean ABR	SD	Range
Standard prophylaxis	8	0.9	1.3	1.47	0.0-4.2
Modified prophylaxis	1	1.6	1.6	NA	1.6-1.6

Source: CSR 251001 Table 70

In the **age group ≥12 to <18 years (n=5)**, where all 5 subjects received standard prophylaxis and 2 also received modified prophylaxis, the mean and median ABRs for modified prophylaxis were slightly higher than for standard prophylaxis. This may be explained by the ABR of 34.55 in one subject during modified prophylaxis.

Table 14. Annualized Bleeding Rate (FAS) – Age Group ≥12 to <18 Years (n=5)

Treatment	N	Median	Mean ABR	SD	Range
Standard prophylaxis	5	13.0	13.4	10.49	1.9-30.3
Modified prophylaxis	2	19.3	19.3	21.56	4.1-34.6

Source: CSR 251001 Table 70

In the **adult population ≥18 years of age (n=89)**, 82 received overall prophylaxis and 13 received on-demand treatment. The median and mean ABR during overall prophylaxis was considerably lower than during on-demand treatment. The ABR was lowest during PK-tailored prophylaxis, however, only 2 subjects were included in this analysis

Table 15. Annualized Bleeding Rate (FAS) – Age Group ≥18 Years (n=89)

Treatment	N	Median	Mean ABR	SD	Range
Standard prophylaxis	80	1.3	3.6	9.35	0.0-78.7
Modified prophylaxis	15	1.2	5.7	8.71	0.0-30.2
PK-tailored prophylaxis	2	1.9	1.9	1.96	0.5-3.3
Overall prophylaxis	82	1.4	3.2	6.70	0.0-52.2
On-demand treatment	13	16.5	18.2	11.17	0.0-31.1

Source: CSR 251001 Table 70

Consumption

Subjects on overall prophylaxis (n=110) received a mean (± SD) of 8.4 (± 1.38) (median: 8.4, range: 3.3-16.6) infusions per month and a mean of 101.1 (± 16.50) (median: 101.2, range: 39.9-198.9) infusions per year. The mean weight-adjusted consumption was 464.2 (± 111.46) IU/kg per month and 5570.7 (± 1337.53) IU/kg per year. The mean weight-adjusted consumption was lowest for the 3 subjects who received PK-tailored prophylaxis (250.9 [± 41.37] IU/kg per month, 3010.3 [± 496.44] IU/kg per year).

Subjects who received on-demand treatment (n=13) received a mean (± SD) of 3.6 (± 2.44) (median: 3.3, range: 0.8-9.3) infusions per month and a mean of 43.1 (± 29.28) (median: 39.4, range: 9.9-111.7) infusions per year. The mean (± SD) weight-adjusted consumption was 199.8 (± 124.18) IU/kg per month and 2397.4 (± 1490.22) IU/kg per year.

During overall prophylaxis, a mean dose of 122.0 (± 134.02) IU/kg of BAX326 was used per bleeding episode (n=659) until resolution of bleed. During on-demand treatment, a mean dose of 82.6 (± 48.21) IU/kg of BAX326 was used per bleeding episode (n=453).

The following tables summarize the Weight-Adjusted Consumption per Year [IU/kg] per Age group in both treatment Cohorts:

Table 83
Consumption of BAX326 per Subject (Secondary Efficacy Outcome) by Age Group 1
(Study 251001: Full Analysis Set)

Age Group= <12 years

Parameter	Statistics	Standard Prophylaxis	Modified Prophylaxis	PK-Tailored Prophylaxis	Overall Prophylaxis	On-Demand
	Min; Max	333.1; 582.0	322.5; 512.9	NA	333.1; 538.4	NA
Weight-Adjusted Consumption per Year [IU/kg]	N	21	5	0	21	0
	Mean (SD)	5347.2 (672.94)	5305.1 (894.19)	NA	5276.1 (560.65)	NA
	Median	5447.6	5412.9	NA	5408.2	NA
	Q1; Q3	4972.6; 5558.5	5162.3; 5926.1	NA	4972.6; 5558.5	NA
	Min; Max	3996.8; 6983.8	3870.0; 6154.3	NA	3996.8; 6460.8	NA

In case a subject changed regimen during the course of the study, then the data from that subject is analyzed under the initial allocated regimen until a change of regimen is recorded. Data recorded after this stage is analyzed under the updated regimen.

[generated by 251001_csra_ex.sas]

Table 83
Consumption of BAX326 per Subject (Secondary Efficacy Outcome) by Age Group 1
(Study 251001: Full Analysis Set)

Age Group= ≥12 years

Parameter	Statistics	Standard Prophylaxis	Modified Prophylaxis	PK-Tailored Prophylaxis	Overall Prophylaxis	On-Demand
	Min; Max	294.6; 1239.9	314.1; 1674.2	208.8; 291.5	208.8; 1243.3	45.4; 506.1
Weight-Adjusted Consumption per Year [IU/kg]	N	87	21	3	89	13
	Mean (SD)	5596.2 (1322.30)	8904.6 (4213.19)	3010.3 (496.44)	5640.2 (1455.64)	2397.4 (1490.22)
	Median	5412.7	7240.3	3026.7	5385.6	2091.4
	Q1; Q3	4984.9; 5948.0	6695.9; 10455.1	2505.8; 3498.3	4984.9; 6021.7	1494.9; 3407.9
	Min; Max	3535.3; 14879.1	3769.1; 20090.9	2505.8; 3498.3	2505.8; 14919.7	544.7; 6073.4

In case a subject changed regimen during the course of the study, then the data from that subject is analyzed under the initial allocated regimen until a change of regimen is recorded. Data recorded after this stage is analyzed under the updated regimen.

[generated by 251001_csra_ex.sas]

Table 85
Consumption of BAX326 per Subject (Secondary Efficacy Outcome) by Age Group 2
(Study 251001: Full Analysis Set)

Age Group= <6 years

Parameter	Statistics	Standard Prophylaxis	Modified Prophylaxis	PK-Tailored Prophylaxis	Overall Prophylaxis	On-Demand
	Min; Max	358.1; 582.0	512.9; 512.9	NA	358.1; 538.4	NA
Weight-Adjusted Consumption per Year [IU/kg]	N	8	1	0	8	0
	Mean (SD)	5440.8 (837.86)	6154.3 (NA)	NA	5375.4 (711.09)	NA
	Median	5493.4	6154.3	NA	5493.4	NA
	Q1; Q3	4810.6; 5818.5	6154.3; 6154.3	NA	4810.6; 5818.5	NA
	Min; Max	4297.4; 6983.8	6154.3; 6154.3	NA	4297.4; 6460.8	NA

In case a subject changed regimen during the course of the study, then the data from that subject is analyzed under the initial allocated regimen until a change of regimen is recorded. Data recorded after this stage is analyzed under the updated regimen.

[generated by 251001_csra_ex.sas]

Table 85
Consumption of BAX326 per Subject (Secondary Efficacy Outcome) by Age Group 2
(Study 251001: Full Analysis Set)

Age Group= ≥6 to <12 years

Parameter	Statistics	Standard Prophylaxis	Modified Prophylaxis	PK-Tailored Prophylaxis	Overall Prophylaxis	On-Demand
	Min; Max	333.1; 532.5	322.5; 493.8	NA	333.1; 470.5	NA
Weight-Adjusted Consumption per Year [IU/kg]	N	13	4	0	13	0
	Mean (SD)	5289.6 (579.49)	5092.8 (874.99)	NA	5214.9 (467.22)	NA
	Median	5408.2	5287.6	NA	5383.0	NA
	Q1; Q3	5196.7; 5548.1	4516.1; 5669.5	NA	5196.7; 5452.5	NA
	Min; Max	3996.8; 6389.4	3870.0; 5926.1	NA	3996.8; 5646.1	NA

In case a subject changed regimen during the course of the study, then the data from that subject is analyzed under the initial allocated regimen until a change of regimen is recorded. Data recorded after this stage is analyzed under the updated regimen.

[generated by 251001_csra_ex.sas]

Table 85
Consumption of BAX326 per Subject (Secondary Efficacy Outcome) by Age Group 2
(Study 251001: Full Analysis Set)

Age Group= ≥12 to <18 years

Parameter	Statistics	Standard Prophylaxis	Modified Prophylaxis	PK-Tailored Prophylaxis	Overall Prophylaxis	On-Demand
	Min; Max	407.1; 582.7	560.0; 871.0	NA	407.1; 692.6	NA
Weight-Adjusted Consumption per Year [IU/kg]	N	5	2	0	5	0
	Mean (SD)	5895.3 (932.81)	8585.8 (2639.20)	NA	6166.1 (1396.15)	NA
	Median	6021.7	8585.8	NA	6021.7	NA
	Q1; Q3	5007.9; 6568.1	6719.6; 10452.0	NA	5007.9; 6603.8	NA
	Min; Max	4885.6; 6993.0	6719.6; 10452.0	NA	4885.6; 8311.7	NA

In case a subject changed regimen during the course of the study, then the data from that subject is analyzed under the initial allocated regimen until a change of regimen is recorded. Data recorded after this stage is analyzed under the updated regimen.

[generated by 251001_csra_ex.sas]

Table 85
Consumption of BAX326 per Subject (Secondary Efficacy Outcome) by Age Group 2
(Study 251001: Full Analysis Set)

Age Group= ≥18 years

Parameter	Statistics	Standard Prophylaxis	Modified Prophylaxis	PK-Tailored Prophylaxis	Overall Prophylaxis	On-Demand
	Min; Max	294.6; 1239.9	314.1; 1674.2	208.8; 291.5	208.8; 1243.3	45.4; 506.1
Weight-Adjusted Consumption per Year [IU/kg]	N	82	19	3	84	13
	Mean (SD)	5578.0 (1344.47)	8938.1 (4395.89)	3010.3 (496.44)	5608.9 (1461.14)	2397.4 (1490.22)
	Median	5399.1	7240.3	3026.7	5383.1	2091.4
	Q1; Q3	4984.9; 5871.7	5382.0; 13369.3	2505.8; 3498.3	4970.7; 5981.6	1494.9; 3407.9
	Min; Max	3535.3; 14879.1	3769.1; 20090.9	2505.8; 3498.3	2505.8; 14919.7	544.7; 6073.4

In case a subject changed regimen during the course of the study, then the data from that subject is analyzed under the initial allocated regimen until a change of regimen is recorded. Data recorded after this stage is analyzed under the updated regimen.

[generated by 251001_csra_ex.sas]

Bleeding Episodes

There were a total of 1149 BEs, of which 693 occurred during overall prophylaxis and 456 during on-demand treatment. By type of prophylaxis, 574 BEs occurred during standard prophylaxis, 111 during modified prophylaxis, and 8 during PK-tailored prophylaxis.

By age group, 29 BEs occurred in the <6-year age group, 37 in the age group ≥6 to <12 years, 128 in the age group ≥12 to <18 years, and 955 in the ≥18-year age group.

The majority of BEs (617 of 1149; 53.7%) were spontaneous, 387 (33.7%) BEs were injury-related, and for 145 (12.6%) BEs the cause was unknown. By treatment regimen, 311 of 617 spontaneous BEs occurred during on-demand treatment and 306 during overall prophylaxis.

Most BEs in the FAS were of moderate severity, 196 (17.1%) BEs were minor, 136 (11.9%) were major, and 2 (0.2%) were life/limb-threatening. The latter two (intracranial bleed, hematuria) occurred during overall prophylaxis in subjects <12 years of age and were reported as unrelated SAEs.

For 1114 of 1149 (97.0%) BEs, treatment with BAX326 was required. Of these 1114 BEs, 660 occurred during overall prophylaxis and 454 during on-demand treatment.

For 9 BEs (for 8 BEs during standard and 1 BE during modified prophylaxis) hospitalization was required.

Analgesics were required for 53 BEs (for 48 BEs during overall prophylaxis and 5 BEs during on-demand treatment)

Control of Bleeding

A mean (± SD) number of 1.8 (± 1.65) infusions were required until bleed resolution. Most bleeds were controlled with 1 infusion (623 of 1112 BEs, 56.0%), for 266 BEs (23.9%) 2 infusions were required, and for 222 BEs (20.0%) at least 3 infusions were required. For overall prophylaxis (n=658 treated bleeds), 342 BEs (52.0%) were controlled with 1 infusion, 154 BEs (23.4%) with 2 and 162 BEs (24.6%) with ≥3 infusions.

Health Related Quality of Life (HR QoL)

All HR QoL analyses were performed on the full analysis set (FAS). Baseline scores are only available for newly recruited subjects who received overall prophylaxis only; no baseline values were reported from transitioning subjects. Scores for the end of the study are available for subjects who received overall prophylaxis only, ondemand treatment only, and overall prophylaxis and on-demand treatment.

The results of the HRQoL measures used in this study (EQ-5D and pain score, SF-36, Peds-QL, Haem-A-QOL, Haemo-QOL) may suggest a better health status in general with less pain and a better quality of life at the end of the study than at baseline.

Pharmacokinetic Outcome Measures

PK analyses were performed for 6 subjects in the Pharmacokinetic Full Analysis Set (PKFAS) who underwent an abbreviated PK study. All 6 subjects who underwent an abbreviated PK study were newly recruited subjects (Cohort 2) ≥18 years of age; two subjects were European and 4 subjects were Asian. The analysis of incremental recovery (IR) at 30 min post-infusion was performed on the FAS (n=115).

The following table gives an overview of the means, medians and ranges of the PK parameters:

In-text Table 14 PK Parameters from Abbreviated PK Study (n=6)				
Parameter	**Mean**	**SD**	**Median**	**Min; Max**
$AUC_{0\text{-}72h}$/Dose [IU.hr/dL:IU/kg]	15.22	3.08	16.07	10.64; 18.55
$AUC_{0\text{-}inf}$/Dose [IU.hr/dL:IU/kg]	17.44	3.63	18.84	12.10; 20.94
$AUC_{0\text{-}72h}$ [IU.hr/dL]	1164.38	248.56	1243.77	793.69; 1420.40
$AUC_{0\text{-}inf}$ [IU.hr/dL]	1335.56	299.83	1459.07	902.07; 1638.52
$T_{1/2}$ [hours]	28.52	4.12	28.67	23.33; 34.73
MRT [hours]	29.97	2.72	30.54	25.93; 34.03
Clearance [dL/kg/hours]	0.06	0.014	0.05	0.05; 0.08
V_{SS} [dL/kg]	1.78	0.42	1.71	1.35; 2.52
C_{max} [IU/dL]	65.70	17.08	68.20	37.80; 84.50
T_{max} [hours]	0.62	0.12	0.58	0.50; 0.78
$IR_{30\ min}$ [IU/dL:IU/kg]	0.85	0.196	0.95	0.50; 1.01

Source: Table 97

The following table shows the IR at 30 minutes post-infusion at baseline and at the end of the study, including the change from baseline:

Table 98
Incremental Recovery at 30 Min for BAX326
(Study 251001: Full Analysis Set)

Visit	Treatment[b]	N	Mean	SD	Median	Q1; Q3	Min; Max
Baseline[a]	Overall Prophylaxis Only	99	0.85	0.211	0.84	0.69; 0.99	0.50; 1.32
	On-Demand Only	3	0.68	0.168	0.73	0.50; 0.82	0.50; 0.82
	Overall Prophylaxis & On-Demand	8	0.85	0.143	0.88	0.72; 0.97	0.64; 1.01
	Overall	110	0.85	0.207	0.83	0.69; 0.98	0.50; 1.32
End of Study	Overall Prophylaxis Only	97	0.84	0.297	0.86	0.70; 1.02	-0.01; 1.47
	On-Demand Only	4	0.94	0.130	0.94	0.84; 1.04	0.79; 1.09
	Overall Prophylaxis & On-Demand	7	0.92	0.158	0.94	0.75; 1.05	0.75; 1.16
	Overall	108	0.85	0.286	0.87	0.71; 1.02	-0.01; 1.47
Change From Baseline to End of Study	Overall Prophylaxis Only	94	-0.02	0.260	0.01	-0.10; 0.12	-1.23; 0.49
	On-Demand Only	3	0.27	0.217	0.27	0.06; 0.49	0.06; 0.49
	Overall Prophylaxis & On-Demand	7	0.06	0.215	0.05	-0.09; 0.19	-0.26; 0.42
	Overall	104	-0.005	0.259	0.02	-0.10; 0.12	-1.23; 0.49

[a]For transitioning subjects: screening visit, for newly recruited subjects: exposure day 1

FIX levels below the limit of quantification were set to 0.5.
Cases with a dosage higher than 120 IU/kg were excluded.

[b]Overall Prophylaxis Only: Subjects who were assigned exclusively to any prophylaxis regimen during the whole study period.

On-Demand Only: Subjects who were assigned exclusively to on-demand regimen during the whole study period.

In subjects <12 years of age, who all received prophylaxis, the mean IR at 30 min postinfusion was 0.72 (± 0.156) at baseline and 0.70 (± 0.219) at the end of the study (mean change from baseline: -0.01 (± 0.205(). This matches the anticipated recovery of 0.7 [IU/dl]/[IU/kg] for pediatric patients <12 years of age in the RIXUBIS Prescribing Information.

In the subjects ≥12 years of age, the mean IR at 30 min post-infusion was 0.88 (± 0.206) at baseline and 0.88 (± 0.289) at the end of the study (mean change from baseline: -0.004 (± 0.271(), which matches the anticipated recovery of 0.9 [IU/dl]/[IU/kg] for patients ≥12 years of age in the RIXUBIS Prescribing Information.

In subjects <6 years of age, the mean IR at 30 min post-infusion was 0.67 (± 0.130) at baseline and 0.63 (± 0.091) at the end of the study (mean change from baseline: -0.03 (± 0.0658), which confirms a tendency toward higher IR in association with increased subject age.

Safety results

A total of 115 subjects were enrolled and treated. The safety evaluation was performed on the FAS comprising these 115 subjects (65 had transitioned from Pivotal Study 250901, 20 from Pediatric Study 251101, and 30 were newly recruited, BAX326 naïve subjects).

Exposure
Subjects in the FAS (n=115) had a mean (± SD) of 252.0 (± 141.64) (median: 254.0, range: 1.0-637.0) BAX326 EDs during the study.

Subjects on overall prophylaxis (n=110) had a mean of 251.0 (± 138.39) EDs.

Subjects on on-demand treatment (n=13) had a mean of 83.6 (± 109.24) EDs.

The 85 subjects who had transitioned from the pivotal/pediatric studies (Cohort 1) had a mean (± SD) of 49.7 (± 15.47) (median: 52.0, range: 5.0-83.0) prior BAX326 EDs.

The 21 subjects <12 years of age had a mean of 256.0 (± 116.44) (median: 225.0, range: 28.0-448.0) BAX326 EDs during the study.

The 19 subjects <12 years of age who had transitioned from the pediatric study (Cohort 1) had a mean of 54.3 (± 4.95) (median: 52.0, range: 50.0-69.0) prior BAX326 EDs.

Of 115 subjects included in the FAS, 106 reached ≥100 BAX326 EDs during the study. Of these 106 subjects, 103 received overall prophylaxis and 3 received on-demand treatment

Adverse Events:

A total of 459 AEs were reported for 85 (73.9%) subjects. This translates to a percentage of 0.3 AEs per infusion (n=28862). Of 459 AEs, 16 in 9 subjects were serious and 443 in 85 subjects were non-serious. None of the 16 SAEs were considered related to IP (= primary endpoint). Of the 443 non-serious AEs, 2 were considered related “positive antibody test (ie, antibodies to rFurin, titer 1:80); see also below) and 441 unrelated.

The following table gives an Overview over the *SAEs*, including severity and the age group in which they occurred

Table 18. SAEs in Study 251001

SAE Preferred Term	Age Group	Severity
Abdominal pain	<6 years	moderate
Duodenal ulcer hemorrhage	≥18 years	severe
Corneal abscess	≥18 years	moderate
Brain contusion	≥6 to <12 years	severe
Extradural hematoma	≥6 to <12 years	severe
Head injury	<6 years	severe
Scrotal hematoma	≥18 years	moderate
Seizure	≥18 years	severe
Transient ischemic attack	≥18 years	moderate
Hematuria (3 events)	<6 years	2 moderate, 1 severe
Renal colic (2 events)	<6 years	moderate
Renal colic	≥18 years	severe
Testicular appendage torsion	≥12 to <18 years	mild

Source: CSR 251001 Table 154, Table 156, Listing 35, narratives in CSR 251001 Section 14.2

In total, there were 16 SAEs in 9 subjects. All SAEs were considered by the investigator and the sponsor to be unrelated to IP. All SAEs were resolved at the time of study completion, with the exception of a severe duodenal ulcer hemorrhage in a 29-year-old subject which resolved with sequelae.

Among the *non-serious AEs* (n=443), the majority was mild (318 AEs), 120 were moderate and 5 were severe. Two non-serious AEs of a positive antibody test (ie, antibodies to rFurin, titer 1:80) in two subjects (1.74% of 115 subjects in the FAS) were considered related to IP. One was considered possibly related, the other probably related. Both AEs occurred in subjects ≥18 years of age:

- A 33-year-old subject had a rFurin antibody titer of 1:80 on Study Day 660 (Month 21), evaluated by the investigator to be of moderate severity and possibly related to IP. A subsequent measurement, on Study Day 981 (Month 33), showed a titer of 1:320. This was also reported as an AE, considered mild and unlikely related. However, at study completion the rFurin antibody test result was negative again and, therefore, considered transient
- A 24-year-old subject had a rFurin antibody titer of 1:80 on Study Day 177 (Month 6), evaluated by the investigator to be mild and probably related to IP. Subsequent measurements on Day 457 (Month 15) and Day 1257 (Month 42), with titers of 1:20 and 1:320, respectively, were also reported as AEs, both considered mild and not related. At study completion the rFurin antibody test result was negative again and, therefore, considered transient

By age group, 7 SAEs (5 moderate, 2 severe) in 2 subjects and 54 unrelated non-serious AEs in 7 subjects occurred in subjects <6 years of age.
Two SAEs (both severe) in one subject and 32 unrelated non-serious AEs occurred in subjects ≥6 to <12 years of age.
One SAE (mild) and 26 unrelated non-serious AEs reported for 5 subjects occurred in the age group ≥ 12 to <18 years of age.

Six SAEs (3 moderate, 3 severe) in 5 subjects and 331 non-serious AEs, of which 2 were considered related to IP, reported for 64 subjects occurred in the ≥18-year age group.

Very common AEs (ie, occurred in more than or equal to 10% of subjects) in the FAS (n=115) were pyrexia (23 AEs in 14 [12.17%] subjects), nasopharyngitis (55 AEs in 25 [21.74%] subjects), and arthralgia (48 AEs in 15 [13.04%] subjects). Another two very common AE in the ≤12-year age group (n=21) were cough (4 AEs in 4 [19.05%] subjects) and upper respiratory tract infection (3 AEs in 3 [14.29%] subjects).

FIX inhibitors

No subject developed an inhibitory antibody to FIX with a titer ≥0.6 BU. The IR of BAX326 remained constant over time which suggests no indication of subclinical inhibitors.

Binding Antibodies

None of the subjects treated in Continuation Study 251001 developed binding antibodies to FIX with confirmed specificity at any time point in the study

Anti-rFurin

Low titer binding antibodies to FIX or rFurin below the limit for the detection of specific antibodies were detected both before as well as after treatment with BAX326 at the lowest detectable titers (i.e., 1:20 or 1:40) in individual subjects at single time points.

However, low antibody titers of 1:20 and 1:40 were within assay variation and too low to be confirmable for specificity. These titers were reported as “indeterminate” because the confirmatory assay was not conducted for those samples. In compliance with current guidelines, only titers of ≥1:80 that were confirmed for specificity in the competition based confirmatory ELISA assay were considered as “positive”. Low-titer antibody results not confirmed for specificity were evaluated as negative.

Four subjects developed a transient antibody to rFurin at single time points during the study that was not detectable at the end of the study. Four subjects developed a transient antibody to rFurin at single time points during the study that was not detectable at the end of the study

Anti-CHO Protein

Antibodies to CHO were not detected in any subjects treated with BAX326.

Thrombogenicity

Prothrombotic markers (prothrombin fragment 1.2, TAT complexes, D-Dimers) were to be assessed in newly recruited subjects at screening and if clinically indicated. None of the abnormal results were found to be clinically significant.

Hypersensitivity

No severe allergic reactions have occurred in any of the subjects treated

Viral Safety

HIV seromarkers were tested at screening and at study completion. Two subjects ⩾18 years of age were HIV positive at screening and remained positive at the end of the study

2.3.3. Discussion on clinical aspects

In accordance with Article 46 of Regulation (EC) No 1901/2006, the final clinical study report of the marketing authorisation holder sponsored study 251001 (BAX326 Continuation Study), which was conducted in compliance with the approved paediatric investigation plan EMEA-001139-PIP01-11-M02, was submitted as a PAM as approved with the PIP decision P/0021/2016 on 29Jan2016.

The continuation study BAX326 investigated the safety, hemostatic efficacy and immunogenicity BAX326 and changes in HR QoL in PTPs with severe and moderately severe hemophilia B who completed either BAX326 Pivotal Study 250901 or BAX326 Pediatric Study 251101 (Cohort 1) as well as in approximately 25 subjects not previously exposed to BAX326 (Cohort 2).

A total of 115 subjects were included in the Full Analysis Set (FAS) and Per Protocol Analysis Set (PPAS). Of these, 65 had transitioned from Pivotal Study 250901, 20 from Pediatric Study 251101, and 30 were newly recruited, BAX326 naïve subjects. Subjects transitioning from Pivotal Study 250901 or Pediatric Study 251101 (Cohort 1) had the option of receiving prophylactic or on-demand treatment. Newly recruited subjects (Cohort 2) could only receive prophylactic treatment.

A total of 110 subjects received overall prophylaxis. This includes 108 subjects on standard prophylaxis, 26 on modified prophylaxis, and 3 on PK-tailored prophylaxis. Thirteen subjects received on-demand treatment. The 3 subjects who underwent PK-tailored prophylaxis were all in Cohort 2, ie, were newly recruited, BAX326 naïve subjects and were ≥18 years of age. In the <12-year age group, all 21 subjects were assigned exclusively to overall prophylaxis (ie, standard prophylaxis (n=21) and modified prophylaxis (n=5).

Most subjects were ≥18 years of age (n=89); 8 subjects were <6 years of age, 13 were ≥6 to <12 years of age, and 5 were ≥12 to <18 years of age, 21 subjects were <12 years of age.

Conclusion on Efficacy:

Treatment of Bleeding Episodes

A mean (± SD) number of 1.8 (± 1.65) infusions were required until bleed resolution. Most bleeds were controlled with 1 infusion (623 of 1112 BEs, 56.0%), for 266 BEs (23.9%) 2 infusions were required, and for 222 BEs (20.0%) at least 3 infusions were required. For overall prophylaxis (n=658 treated bleeds), 342 BEs (52.0%) were controlled with 1 infusion, 154 BEs (23.4%) with 2 and 162 BEs (24.6%) with ≥3 infusions.

Annualized bleeding Rate

The ABR was lower during prophylactic treatment than during on-demand treatment. While the median ABR was 16.5 (mean: 18.2 (± 11.17) in the on-demand group (n=13), it was only 1.3 (mean: 3.3 (± 6.67)) in the overall prophylaxis group (n=108). By type of prophylaxis, the ABR was lowest during PK-tailored prophylaxis (n=2): median ABR of 1.9 (mean: 1.9 (± 1.96). However, only 2 subjects were included in this analysis. The next lowest mean ABR occurred during standard prophylaxis (n=106, median: 1.3, mean ABR of 3.6 (± 8.72)). During modified prophylaxis (n=22), the median ABR was 1.4 (mean: 5.9 (± 9.79)).
Mean and median ABRs for modified prophylaxis were generally slightly higher than for standard prophylaxis. However, the applicant does not intend any modifications of the treatment scheme and the final study report of the extension study cannot serve as basis for any changes with this regards. The outcomes are therefore acceptable since no alteration of the efficacy profile can be derived.

The mean/median ABR in the age group of >12 to <18 is unusually high. This is mainly driven by two subjects, one in each treatment group (standard prophylaxis and modified prophylaxis). However, it should also be taken into account that the overall number of subjects in this age group is very limited (standard prophylaxis: N=5 and modified prophylaxis: N=2). Nevertheless, such high bleeding rates under prophylactic treatment are unusual and the applicant should describe these two patients in more detail and provide possible reasons behind this finding (e.g. target joints…).

Consumption

Subjects on overall prophylaxis (n=110) received a mean (± SD) of 8.4 (± 1.38) (median: 8.4, range: 3.3-16.6) infusions per month and a mean of 101.1 (± 16.50) (median: 101.2, range: 39.9-198.9) infusions per year. The mean weight-adjusted consumption was 464.2 (± 111.46) IU/kg per month and 5570.7 (± 1337.53) IU/kg per year.
During overall prophylaxis, a mean dose of 122.0 (± 134.02) IU/kg of BAX326 was used per bleeding episode (n=659) until resolution of bleed.

Subjects who received on-demand treatment (n=13) received a mean (± SD) of 3.6 (± 2.44) (median: 3.3, range: 0.8-9.3) infusions per month and a mean of 43.1 (± 29.28) (median: 39.4, range: 9.9-111.7) infusions per year. The mean (± SD) weight-adjusted consumption was 199.8 (± 124.18) IU/kg per month and 2397.4 (± 1490.22) IU/kg per year.
During on-demand treatment, a mean dose of 82.6 (± 48.21) IU/kg of BAX326 was used per bleeding episode (n=453).

Health Related Quality of Life Outcome Measures

The results of the HRQoL measures used in this study (EQ-5D and pain score, SF-36, Peds-QL, Haem-A-QOL, Haemo-QOL) show a better health status with less pain and a better quality of life at the end of the study than at baseline.

Pharmacokinetic Outcome Measures

The PK parameters assessed can be deemed are comparable with those assessed in Pivotal Study 250901 with no major discrepancies with regards to key PK parameters.

The mean IR at 30 minutes post-infusion did not change over time. Subjects <12 years of age had a mean IR of 0.72 (± 0.156) at baseline and 0.70 (± 0.219) at the end of the study. Subjects ≥12 years of age had a mean IR of 0.88 (± 0.206) at baseline and 0.88 (± 0.289) at the end of the study which overall is in line with the SmPC for Rixubis (<12 years 0.7 [IU/dl]/[IU/kg]; ≥12 years 0.9 [IU/dl]/[IU/kg]).

Overall the data set provided indicates that Rixubis is an effective treatment for adult and paediatric patients.

Conclusion in Safety:

459 AEs occurred in 85 (73.9%) subjects, of which 16 in 9 subjects were serious and 443 in 85 subjects were non-serious. None of the 16 SAEs were deemed related to IP (= primary endpoint) by the investigator and the sponsor.
Of the 443 non-serious AEs, two AEs of a positive antibody test (ie, antibodies to rFurin, titer 1:80) in two subjects were considered related. Both AEs occurred in subjects ≥18 years of age, and by the time of study completion, the rFurin antibody tests results in these two subjects were negative again and, therefore, considered transient.

No binding antibodies to FIX were developed and no antibodies to CHO were detected in any subject at screening or after treatment.

Four subjects developed a transient antibody to rFurin at single time points during the study that was not detectable at the end of the study. (Two of these were reported as related, non-serious AEs; see above.) All other subjects tested negative for binding antibodies with confirmed specificity against rFurin during the study.

No significant treatment-related changes in laboratory values or vital signs were recorded.

No deaths, no serious adverse events (SAEs) considered related to IP, no severe allergic reactions and no thrombotic events occurred during or after treatment.

Overall, from the data set provided, an adequate safety and tolerability profile of BAX326 in children and adults can be concluded. No new safety aspects others than those observed in the course of the MAA became apparent.

3. Rapporteur's overall conclusion and recommendation

As Post authorisation measure the MAH submitted the final clinical study report of the deferred Continuation Study 251001 approved with the PIP decision P/0021/2016 on 29Jan2016.
The MAH did not discuss or include a separate overview over the paediatric data only obtained between MAA and the current submission. However the data presented in the final study report did not indicate any new safety or efficacy aspects which may alter the benefit risk profile. The benefit risk profile therefore remains positive in the licenced indication for the adult and paediatric population. The MAH concludes that data do not require an update of the Product Information. This can be supported since the information obtained in the final study report is already covered by the currently approved PI.

However, the mean/median ABR in the age group of >12 to <18 is unusually high. This is mainly driven by two subjects, one in each treatment group (standard prophylaxis and modified prophylaxis). However, it should also be taken into account that the overall number of subjects in this age group is very limited (standard prophylaxis: N=5 and modified prophylaxis: N=2). Nevertheless, such high bleeding rates under prophylactic treatment are unusual and further clarification should be provided.

☒ **Fulfilled:**

No regulatory action required. However, further clarification on two subjects with unusual high bleeding rates under prophylactic treatment should be provided.

4. Additional clarification requested

The mean/median ABR in the age group of >12 to <18 is unusually high. This is mainly driven by two subjects, one in each treatment group (standard prophylaxis and modified prophylaxis). Although the overall number of subjects in this age group is very limited (standard prophylaxis: N=5 and modified prophylaxis: N=2), such high bleeding rates under prophylactic treatment are unusual. The applicant should therefore describe these two patients in more detail and provide and discuss possible reasons behind this finding (e.g. target joints…).

MAH responses to Request for supplementary information

N/A